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CONTENTS

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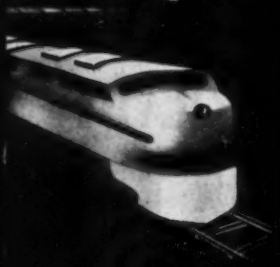

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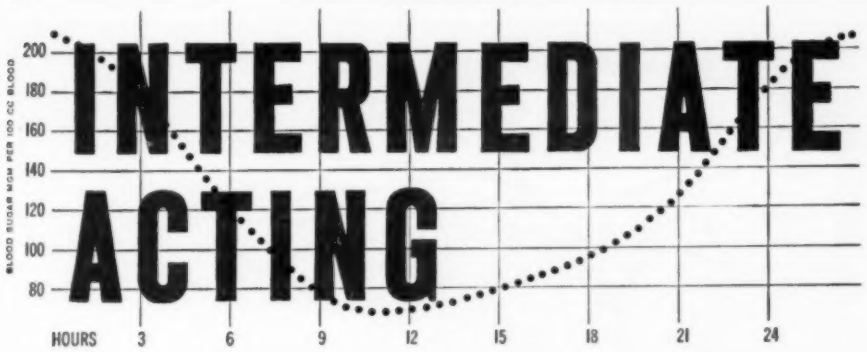

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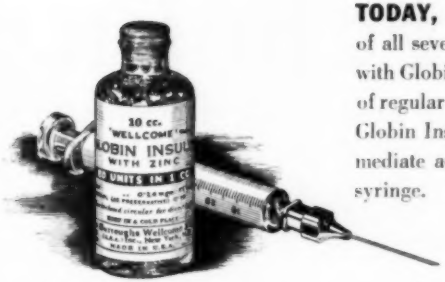

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
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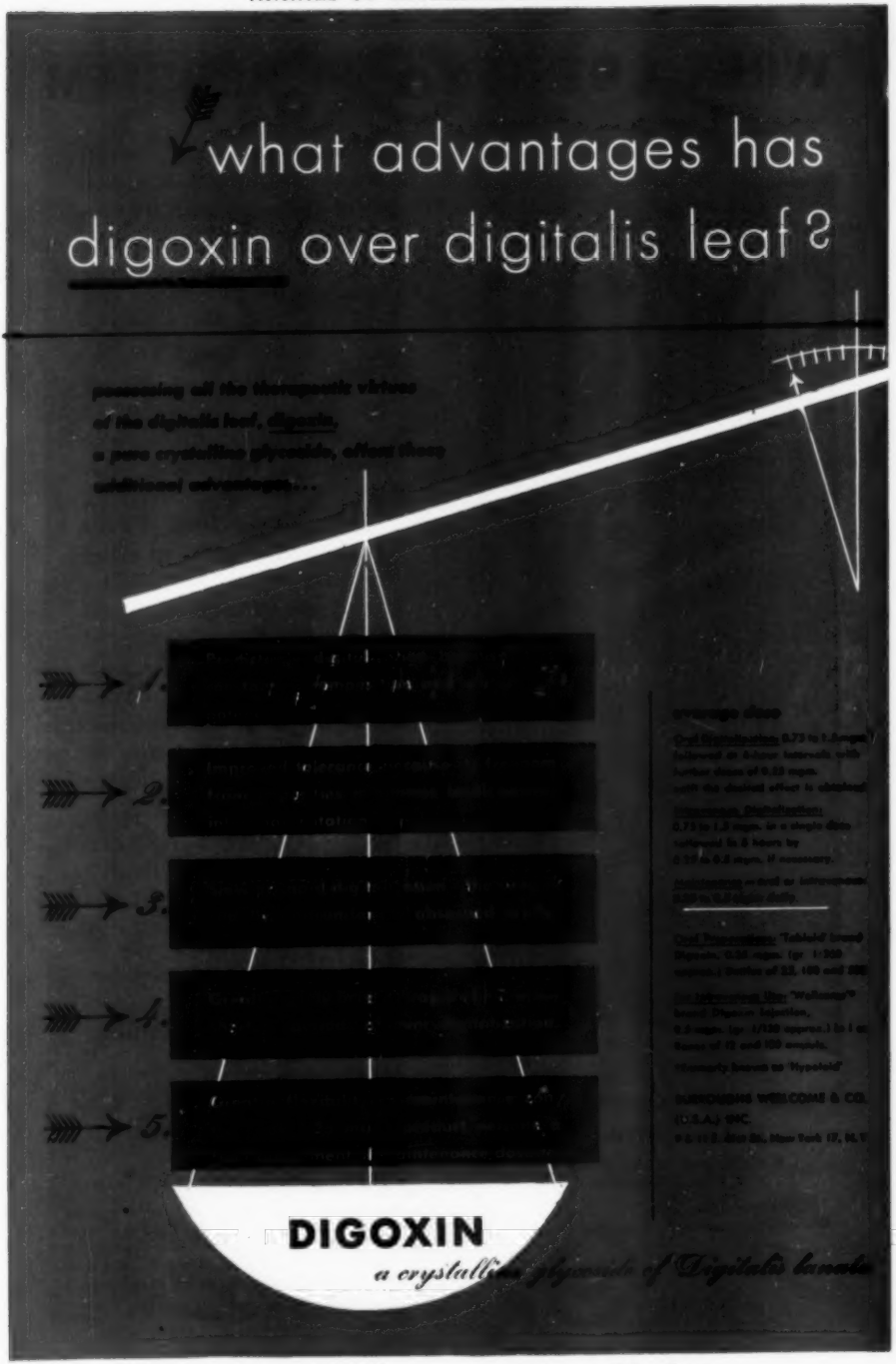
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ANNALS OF
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THE NATURAL OCCURRENCE OF ANTITHYROID COMPOUNDS AS A CAUSE OF SIMPLE GOITER*

By E. B. ASTWOOD, M.D., F.A.C.P., *Boston, Massachusetts*

As more is learned about the thyroid gland the more plausible is the concept that goiter is a compensatory enlargement consequent to some interference with normal thyroid function. The subject of continuing debate, however, relates to the relative importance of the numerous factors which are known to be or which are suspected of being concerned in thyroid hormone synthesis. While there can be no question of the fact that iodine is an essential dietary ingredient; and, while it is well established that iodine deficiency is a cause of simple goiter, there is reason to believe that goiter is not always due to this cause alone. The observation that certain types of food may lead to goiter, coupled with the recent demonstration that virtually hundreds of pure chemical substances are highly effective goitrogens, suggests that a reëxamination of the problem might be worthwhile. If an active antithyroid agent be concerned in the occurrence of endemic or sporadic goiter in man, the most likely avenue of entry into the body is with the food, and among the foods which might contribute such a substance foods of vegetable origin appear to be the most likely. It will be our purpose here, therefore, to consider the possibility that goiter may sometimes be caused by the consumption of foods and especially of plant foods containing antithyroid compounds.

SOME OLDER THEORIES

The idea that goiter might be caused by positive goitrogenic influences is not new; theories involving one or another substance as the etiologic agent date from the time of the earliest descriptions of goiter. So numerous and

*John Phillips Memorial Lecture delivered at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 30, 1949.

From the Joseph H. Pratt Diagnostic Hospital and the Department of Medicine, Tufts Medical School.

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varied are these theories that their evaluation taxes one's interpretive capacity as the data on very few other subjects do. As long ago as 1867, Saint-Lager,[1] in reviewing the theories of goitrogenesis, listed the causes under 42 different categories, each of which was extensively documented. Some of these which are among the more pertinent to the present discussion are summarized in table 1. It is interesting to note that several inorganic

TABLE I

Some Causes of Goiter Cited by St. Lager in 1867

Waters Containing Excessive Quantities of:		
Suspended matter	Gypsum	Organic matter
Calcium	Silica	Carbonic acid
Magnesium	Fluoride	Volcanic ash
Sulfurous substances	Barium	Coal and metal extractives
Waters Deficient in:		
Oxygen	Iodine	Phosphate
Carbonic acid	Bromine	
Consumption of:		
Vegetables	Pork	Alcohol
Milk	Fat foods	Certain cooking salts

substances which have received quite wide attention in the past two decades are listed; iodine deficiency and dietary factors, including the consumption of vegetables, are also included.

More modern methods of observation and the use of laboratory technics have not entirely resolved the problem. McCarrison,[2] in 1937, after a lifetime's study of goiter concluded that the causes of goiter could be summarized under four headings (table 2). Thus, 70 years after the time of Saint-

TABLE II

Causes of Goiter According to McCarrison—1937

1. Faulty diet:
   - A. Excess of: fat, fatty acids, and lime
   - B. Deficiency of: iodine, vitamins A and C, protein, phosphate
   - C. Goiter-producing substances—cyanogen compounds
   - D. Lack of antigoitrogens present in green grass, alfalfa, steamed cabbage juice, sprouted legumes, and carrots
2. Chemical substances

   Calcium, boron, silica, tellurium, organic acids, amines, cyanides, coal tar
3. Unsanitary conditions
4. Infections

Lager, positive goitrogenic influences retained a more prominent position in McCarrison's opinion than other factors such as iodine deficiency. The inclusion in this summary of certain types of food and certain chemical substances which might occur in foodstuffs attests the fact that food as a cause of goiter has continued to be investigated over the intervening years.

A careful analysis of the earlier experiments on food-goiter do not at present make it possible to decide which foods are, with certainty, goitrogenic. So many factors enter into experiments of this type that it is not surprising that conflicting views and contradictory results marked these earlier attempts to define the influence of foodstuffs on goitrogenesis. The importance of controlling the iodine intake was not recognized, nor was it realized that the health and age of the test animals and the environment could modify the result. Even today one cannot be too sure that experiments are free from fault, but it might be well to consider certain factors which aid in interpreting experiments designed to study goitrogenic influences.

Physiologic Factors

An enlarging thyroid gland may indicate an increasing rate of hormone formation or it may indicate the reverse—a decreased rate which has evoked compensatory hypertrophy and hyperplasia. It may be only with great difficulty that these two opposite situations can be distinguished for morphologically the changes are the same. In each case the enlarging gland shows increased vascularity, the cells become larger and encroach upon the follicular lumina, and the colloid becomes so dilute that it may not stain with the usual dyes. Likewise, both the activated and the inhibited gland exhibits a loss of its store of protein-bound iodine. To distinguish between the two opposite situations, it would be necessary to use special criteria such as the rate of metabolism, the concentration of thyroxine in the blood, or tracer studies with radioiodine.

Under conditions of good health and rapid growth the thyroid tends to be relatively enlarged and activated; it is further activated in cold environments and after the administration of thyrotropin. It has been well established that thyroid atrophy and underfunction are associated with malnutrition and chronic ill health; a warm environment and the administration of various toxic substances likewise induce thyroid atrophy. If the adverse influence, whatever it may be, is severe enough, the thyroid suffers to an extent almost as extreme as that which follows hypophysectomy. Indeed, these factors which activate and depress the gland seem to do so by modifying the thyrotropic function of the pituitary gland.

It is likely that some of the studies on goiter in the past might be interpreted in terms of these modifications in the functional states of the thyroid gland. Perhaps a diet which may have been considered slightly goitrogenic may actually have been merely more nutritious than the control diet; the larger glands from the "experimental" diet may have been the normal ones and the "control" thyroids may have been atrophic. This factor may have contributed to the impression that high protein diets are goitrogenic. Certain environmental influences which have been found to increase the size of the thyroid may have a similar explanation.

Even when a highly potent goitrogen is administered, the extent of the

enlargement of the thyroid is dependent upon other factors. Undernutrition, toxic agents, and warm environments suppress the growth of the goiter. Rapid body growth, a good diet, and a cool environment are conducive to maximal rates of thyroid enlargement. An extreme example of this type of influence is to be observed when full cretinism is induced in rats by the administration of propylthiouracil from the time of birth. In the face of this extreme degree of thyroid deficiency the thyroid may hardly enlarge at all. It is as if the pituitary or the thyroid becomes unresponsive if complete athyreosis is induced at an early age. This situation seems similar to that described in endemic cretinism when goiter may sometimes be absent even though thyroid function is minimal or absent.

There are doubtless other factors which should be considered, such as, for example, the absorption and excretion of iodine and factors which might alter iodine metabolism. Recent studies of Riggs[3] have clearly shown that dogs excrete iodide very slowly and in this respect they differ greatly from man. Presumably the dog, in holding on to iodide so avidly, might require a correspondingly smaller iodide intake. Furthermore, the consumption of large quantities of chloride or bromide causes an increased rate of loss of iodide in the urine and consequently these and perhaps other anions could contribute to iodide deficiency by their effects upon the kidney. Thus, there might be a logical explanation for the goitrogenic influence of drinking waters which contain large amounts of various salts, and for the increased iodine requirement of animals fed on diets to which one or another electrolyte is added in excess. Unfortunately, little is known about factors which influence iodide excretion in other animals and man.

Goitrogenic Effect of Certain Plants

Wide interest in the possible goitrogenic influence of certain vegetable foodstuffs dates from the studies of Chesney, Clawson, and Webster.[4] Goiter was unexpectedly encountered in rabbits which were being maintained in the laboratory for other purposes, and these workers made detailed observations on the phenomenon. They finally concluded that the goiter was due to cabbage which formed the major part of the dietary intake.

Within a few years these findings had been confirmed from several quarters. Marine and his co-workers in New York did extensive studies on the nature of the active ingredient of cabbage and extended the field by showing that other related plants such as brussels sprouts, cauliflower, and steamed turnip root were also goitrogenic. Mangel root was found to have a slight effect.[5] Marine and his co-workers tackled the problem with enthusiasm; they were apparently able to reproduce the goiter with ease, and large goiters developed in incredibly short periods of time. They stated, for example, that palpable goiters would develop in 10 to 15 days when steamed cabbage was fed. By 1932, Marine, Bauman, Spence, and Cipra[6] concluded

that the active ingredient was an organic cyanide and that goiter could readily be induced with acetonitrile.

Many subsequent investigators have been unable to induce goiter consistently by feeding cabbage. For example, Spence, Walker, and Scowen [7] in continuing the study of goiter induction by cabbage and by acetonitrile encountered difficulty. Often, cabbage failed to cause any goiter at all and Spence suggested, as had Marine, [8] that certain foods contained antigoitrogens. He also found that small amounts of iodine would prevent goiter formation. Spence, [9] in 1933, made the very interesting observation that methylcyanide was less goitrogenic for chickens than for rabbits and that correspondingly chickens failed to convert the acetonitrile to thiocyanate as did rabbits. This observation appears to be the first which incriminates thiocyanate in this problem. It is unfortunate that in one experiment, presumably in four rabbits, thiocyanate had been found inactive.[10] Perhaps it was for this reason that the interesting thiocyanate lead was not followed up. Its goitrogenicity was not discovered until Barker's observations on man two years later. [11]

Meanwhile, cabbage goiter as an entity was readily confirmed by McCarrison in India. [12] He also found acetonitrile to be effective [13] and noted very striking goitrogenesis from soya beans and peanuts even when large iodine supplements were added.[13, 14] Indeed, as an example of the difficulty one encounters in trying to interpret these findings, pigeons were observed to develop goiter as a result of iodine administration alone. [13]

The year 1933 marked the appearance of the first of an extensive series of studies on "cabbage goiter" from Duneden, New Zealand. Hercus and Aitken [15] found that cabbage feeding sometimes gave rise to small goiters in rabbits but often no effect was observed. Far more consistent results were forthcoming when other brassica plants were employed. [16] Turnip roots produced goiter in two out of 14 rabbits after 60 days of feeding. Rats were soon found to be more suitable than rabbits and when they were fed brassica seed for 30 days, goiter resulted with regularity. While wheat and steamed rape seed were inactive, unheated rape seed and cabbage seed, as well as the steamed seeds of white and black mustard, were highly goitrogenic. Hercus and Purves [16] cited the observation of goiters weighing as much as 202 grams in lambs fed on turnip. In table 3 are listed some of the vegetable foodstuffs which have caused goiter in laboratory animals.

The discovery of the goitrogenicity of rape seed permitted careful studies on the mechanism of action. Prior to this, goiter production from cabbage and related plants was a variable and inconstant phenomenon. The incorporation of rape seed into an otherwise normal diet permitted the animals to thrive; the use of rats made it possible to observe larger numbers of animals and facilitated operative procedures. In 1941 Kennedy and Purves [19] and Griesbach [21] showed that the hyperplastic changes in the thyroid were associated with cellular changes in the pituitary similar to those which follow thyroidectomy. Furthermore, it was shown [22] that no goiter developed if

TABLE III

Vegetables Found to Be Goitrogenic in Laboratory Animals

Cabbage	Chesney, Clawson, and Webster [4]	1928
Brussels sprouts and cauliflower	Marine, Bauman, and Cipra [5]	1929
Kohlrabi	Stiner [17]	1933
Soy bean and peanut	McCarrison [14]	1933
Turnip and seeds of: mustard, rape, and cabbage	Hercus and Purves [16]	1936
Radish	Indina [18]	1940
Seeds of: rutabaga, chou moellier, soft and hard turnip	Kennedy and Purves [19]	1941
Kale, mangel, red cabbage, lentils, and peas	Blum [20]	1942

the hypophysis were removed. Later it was found [23] that excess iodine only partly suppressed the goiter, while thyroxine in physiological doses completely inhibited the thyroid enlargement.

These experiments clearly established that the mechanism of the goitrogenesis from rape seed is the same as that later elucidated for the sulfonamides and thioureas; that is, the primary effect is one of thyroid inhibition. The brassica seed, like the thioureas and sulfonamides, inhibits thyroid hormone synthesis. As a consequence of this, thyrotropin is secreted in larger quantities from the pituitary and compensatory hyperplasia of the suppressed thyroid is the result. This effect came to be known as antithyroid and the agents responsible, antithyroid compounds. The experiments of the New Zealand workers made it a most likely probability that the brassica seed contained an antithyroid compound and this later proved to be the case.

GOITER FROM PURE CHEMICAL SUBSTANCES

Another major contribution to the cause of goitrogenesis was made in 1941. From two laboratories in Baltimore there appeared almost simultaneously the discovery of two chemical substances which would cause goiter in rats. Richter and Clisby [24] had used phenylthiourea (figure 1) for taste studies in rats and had noted that sometimes this compound caused a graying

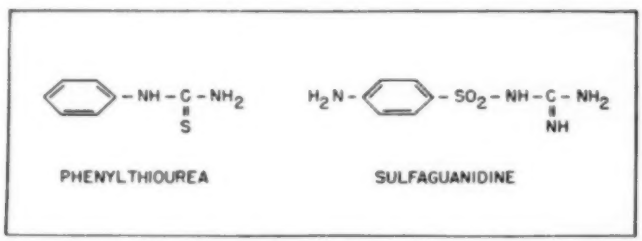

FIG. 1. The superficial structural similarity of the first two antithyroid compounds is illustrated. Phenylthiourea found to be goitrogenic by Richter and Clisby [24] was later shown to owe its activity to the thiocarbonamide grouping; the goitrogenic activity of sulfaguanidine discovered by MacKenzie, MacKenzie, and McCollum [25] proved to be a property of the aromatic amine group.

of the fur. While investigating this they made the further discovery that the compound gave rise to thyroid enlargement. MacKenzie, MacKenzie, and McCollum [25] were employing sulfaguanidine (figure 1) to inhibit bacterial growth in the intestinal tract for studies on nutrition. They observed that rats fed on diets containing sulfaguanidine developed marked thyroid enlargement in a short period of time. They showed clearly that the goiter could not be prevented by iodine but was completely inhibited by small amounts of thyroxine. MacKenzie and MacKenzie [26] then showed that other sulfonamides were goitrogenic and that thiourea itself was a highly effective goitrogen. Kennedy [27] in attempting to elucidate the nature of the goitrogen in rape seed considered that it might be allylthiourea and, therefore, tested this compound in rats. It, too, was found to be effective in causing thyroid enlargement.

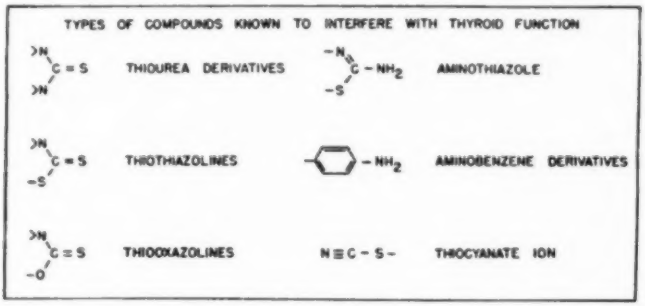

FIG. 2. The numerous chemical compounds now known to interfere with thyroid function owe their biological activity to one or another of these groupings.

Extensive studies by MacKenzie and MacKenzie [28] and somewhat similar ones by Astwood, Sullivan, Bissell, and Tyslowitz [29] led to the concept that compounds of these types inhibit thyroid hormone synthesis. The goiter develops as a secondary reaction; it represents the compensatory hyperplasia which is consequent to the hypothyroidism induced by the inhibitory agent. Further investigations into the chemical nature of the effective compounds showed that the first two compounds discovered in the Baltimore laboratories represented two distinct classes of chemical agents. [30] Sulfaguanidine proved to be a member of a large class of compounds which owe their goitrogenicity in rats to the presence of a free or potentially free aromatic amine group. Phenylthiourea, on the other hand, was active by virtue of the presence of a thiocarbonamide radicle; a very large group of compounds of this type proved to be goitrogenic and within this series some highly active substances were subsequently to be encountered. The several types of compound which are now known to interfere with thyroid function are shown in figure 2. MacKenzie and MacKenzie [26] had shown that sulfa-

guanidine was not goitrogenic in chicks; this observation, later substantiated by VanderLaan and Bissell, [31] further differentiated the two classes of goitrogens. The aminobenzene derivatives apparently have little or no effect in man and certain other animals, while the thiocarbonamides seem to be effective in all species of vertebrate in which they have been tested.

Meanwhile, it had been noted that though potassium thiocyanate had been found to cause goiter in man, it could not readily be caused to do so in the rat. This discrepancy was resolved when it was found that thiocyanate is only goitrogenic when the dietary iodide is low—its effect was completely abolished by adding iodide to the diet. [39] It is now known that thiocyanate owes its goitrogenicity to a unique effect upon the thyroid gland; it prevents the gland from concentrating iodide ion. [32, 43] This iodide ion-concentrating mechanism is of great importance to a normal rate of hormone synthesis when the circulating iodide is low, but when there is an abundance of iodide in the blood, enough of it enters the thyroid gland by diffusion to meet the gland's requirements.

Compounds Known to Occur in Plants Which Might Be Goitrogenic

The extensive literature on the chemical constituents of plants is almost completely devoid of any reference to compounds of the types which are now known to be effective antithyroid agents. There are a variety of substances, however, which might properly come under suspicion, and among these are various aromatic amines, the mustard oils or organic isothiocyanates, thiocyanate ion, and the organic cyanides or nitriles.

Aromatic amines or aminobenzene derivatives of certain types cause goiter when administered to some animals and not others. The rat, mouse, and dog are affected by these compounds, whereas the chick and man are not influenced to a significant degree. The derivatives which are effective in the rat include numerous sulfonamides, and such compounds as diaminobenzil, diaminodiphenylmethane, various para-amino substituted aromatic sulfides and sulfones, and to a slight degree para-aminobenzoic acid. The fact that the human thyroid has not been shown to be influenced by compounds of this type makes it unlikely that aromatic amines of vegetable origin are of importance in human goiter.

The mustard oils or organic isothiocyanates have never been shown to exert a goitrogenic effect. They are such highly irritating substances that only minute amounts can be administered without grave effects upon the well being of the test animals. However, they are widely distributed in the vegetable kingdom and are found in especial abundance in the mustards and their close relatives where they occur in the form of glycosides from which the free isothiocyanate is liberated by enzymatic action. The reason for suspecting isothiocyanates is their close chemical relationship to agents of known effectiveness. In the presence of ammonia they readily give rise to

monosubstituted thioureas (figure 3), and the corresponding disubstituted thioureas are formed if they react with amines. It is conceivable that simple reactions such as these could take place during the process of preparing the food for eating or during mastication or digestion.

Thiocyanate ion also occurs in a great variety of plants; it has been found in considerable quantity in the mustard family but it also occurs in many other types of plant. There is said to be enough present in tobacco smoke to cause a detectable increase in the thiocyanate content of the blood, saliva, and urine of persons who use cigarettes. Large amounts are said to be found in the milk of cows fed on brassica seed and in the urine of man after eating cabbage. The known effect of thiocyanate upon the iodide ion-concentrating

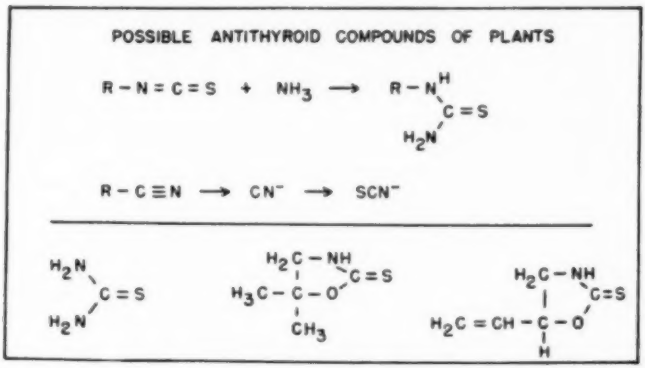

FIG. 3. Organic isothiocyanates or mustard oils readily form substituted thioureas on contact with ammonia or amines. The nitriles or organic cyanides give rise to cyanide ion in the body and this in turn is converted to thiocyanate. The three compounds in the lower part of the figure, thiourea, 5,5-dimethyl-2-thiooxazolidone, and L-5-vinyl-2-thiooxazolidone, have been detected in plants and are effective antithyroid compounds.

mechanism of the thyroid properly suggests that the consumption of foods containing this substance might contribute to the development of goiter.

There is some doubt, however, that there is a sufficient concentration of free thiocyanate in plant foods to have a significant effect. In examining this possibility, VanderLaan and VanderLaan [34] tested the effect of single doses of ground rape seed and cabbage seed, in quantities as large as a stomach full, on the thyroid to blood iodide ratio in the rat. No thiocyanate effect could be detected though their method could have shown the presence of as little as a tenth of a milligram. It is further possible, however, that thiocyanate may occur in plants in a combined form from which it would be liberated only after enzymatic action as in the case of the mustard oils.

The part played by thiocyanate in sporadic and endemic goiter must remain undecided at present, but its rôle as a cause of goiter is worthy of further exploration.

Nitriles and cyanogenetic glycosides are common and widely distributed plant constituents. As mentioned above, several nitriles have been observed to cause goiter in rabbits, [6] and, as already pointed out, these substances could give rise in the body to free cyanide ion which would then be converted to thiocyanate by the well-known detoxication mechanism [9] (figure 3). The fact that those who were successful in causing goiter in animals by the administration of these cyanides, and especially acetonitrile, also found the effect to be inhibited by added iodine would support the thought that the action on the thyroid was due to this transformation to thiocyanate. Furthermore, the influence of certain diets in increasing the blood and urine content of thiocyanate might be attributed to this conversion.

Thioureas were naturally suspected as possible goitrogens in food, but their rôle remains to be determined. Two plants are claimed to contain a thiourea. Thiourea itself was detected in *Laburnum anagyroides*,[35] and benzylthiourea has been isolated from the seeds of the tropical pawpaw (*Carica papaya*).[36] The possibility mentioned above of the formation of thioureas from isothiocyanates on treatment with ammonia seems not to have been entirely excluded in these two investigations. It is still uncertain, therefore, whether plants contain thiourea derivatives.

A Reinvestigation of Food Goiter

Investigations in our laboratory on the influence of foods were a natural outgrowth of studies on antithyroid compounds and date from 1943. After a number of compounds had been evaluated by rat tests for their possible antithyroid activity a relatively simple assay method was standardized for this purpose. [37] The substances were admixed with the food and administered to young rats for 10 days. Relatively large doses induced significant increases in thyroid weight while smaller quantities reduced the thyroid iodine content. This method or minor modifications of it was used in several laboratories for the evaluation of many hundreds of compounds. [38, 39] It seemed at that time that this technic would permit a thorough reëvaluation of the food-goiter problem, and to that end rats were fed for 10 days on a variety of vegetable foodstuffs. [40] The results were entirely inconclusive; no thyroid enlargement was observed, and while the iodine content of the thyroid glands was reduced somewhat the magnitude of the change was not greater than that which followed the feeding of a low iodine diet. Further progress had to await the development of better technics.

When several different compounds had been used clinically for the treatment of hyperthyroidism, it became apparent that their relative activities in man must be quite different from that which had been predicted by animal assay. For example, in France aminothiazole [41] was found to be highly antithyroid for man, whereas its activity in the rat had proved to be quite low [30]; later, propylthiouracil, which was 11 times as active as thiouracil in the rat, was found to be not nearly so active in man. These discrepancies

pointed up the need for a method of testing antithyroid compounds directly in man. Radioactive iodine made such a method possible. [42] The course of radioiodine collection by the thyroid gland of normal human subjects is regular and predictable; when a single dose of an antithyroid compound is given, the accumulation rate is temporarily slowed or stopped altogether. It is thus possible to compare the effectiveness of different compounds in normal people, and when this was done man was found to differ widely from the rat. For example, thiourea and propylthiouracil were approximately equal in antithyroid activity when tested in man, whereas the rat test showed propylthiouracil to be about 100 times as active as thiourea. Contrariwise, methylmercaptoimidazole was only a little more active than thiouracil in rats while it proved to be 100 times as active in man. [43]

It was obvious, therefore, that a food which might not be goitrogenic in rats might affect man and vice versa, and the desirability of using the human being to study the causes of human goiter was apparent. The method described above was therefore applied to foods.[44] A tracer dose of radioiodine was given and the rate of its collection by the thyroid was determined during the next hour or two. The subject was then enticed to eat a single item of diet in as large an amount as possible. The subsequent course of iodine accumulation in the thyroid gland showed whether or not the food contained a significant quantity of an anthyroid compound. Many foods were found to have little or no effect, some inhibited slightly, while a few were strongly inhibitory (figure 4).

From among a series of 61 different foodstuffs which had been tested in normal human subjects the yellow turnip (Swede or Rutabaga) was first selected for fractionation because of its relatively high activity and ready availability. Simple watery extracts of ground turnip contained a substance which would inhibit thyroid function in either rat or man when tested with radioiodine. After the aqueous extract was concentrated by evaporation, the active material could be extracted from the water by means of ether. Further purification led to the isolation of a pure crystalline compound which proved to be L–5–vinyl–2–thioöxazolidone [45]; the structure established by synthesis [46] is shown in figure 3. This substance proved to be about one-fifth as active as thiouracil in the rat and to have about the same activity as thiouracil in man. The quantities isolated made it highly likely that it represented the major, if not the only, antithyroid agent of turnips. It was found to be present in still higher concentrations in the seeds. This same substance was identified in the seeds of cabbage, rape, and kale, and spectroscopic evidence indicated its presence in the seeds of other brassicae, including Chinese cabbage, kohlrabi, brussel sprouts, and broccoli; it was not detected in various types of mustard seed, cauliflower seed, or in the radish, nor could it be obtained from the edible portions of cabbage, kale, broccoli, or cauliflower.

The thioöxazolidone appears to exist in the plant in a combined form from which it is liberated by enzymatic action in aqueous solution. Boiling of the uncrushed seed or root renders the material biologically inert. Aque-

ous extracts of the preheated turnip or seed contain the supposed combined form, for the compound appears upon treatment with a small amount of unheated plant tissue or upon standing in the presence of a protein fraction from the plant. The nature of the combined form or precursor has not yet been elucidated.

The possibility that a thioöxazolidone might account for the goitrogenicity of some of the brassica plants had not been previously entertained, but it is interesting to note that a related compound, 5,5-dimethyl-2-thioöxazolidone had previously been isolated from the seeds of Conringia or hare's ear mustard, [47] a plant of another genus of the Cruciferae.

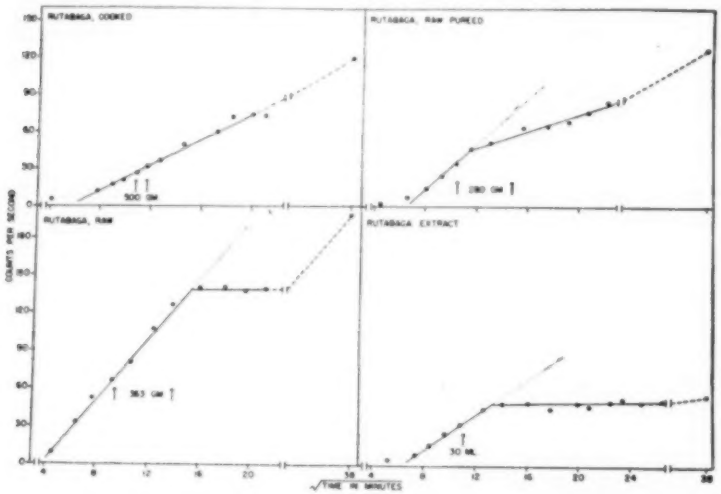

FIG. 4. Tests on cooked and raw rutabaga and on a rutabaga extract in normal human subjects using radioiodine. The cooked vegetable had no effect and the course of radioiodine collection by the thyroid gland did not deviate from the expected straight line. A moderate degree of inhibition was observed with 280 grams of raw rutabaga, 363 grams caused a complete but temporary inhibition, while 30 milliliters of extract inhibited completely for 24 hours (from Greer and Astwood [44]).

It would be instructive if one could reinterpret the literature on food-goiter in the light of these recent developments, but, unfortunately, there is still insufficient information to permit a full understanding. The cause of cabbage goiter remains somewhat in doubt, for while cabbage seeds contain adequate quantities of vinylthioöxazolidone to account for goiter if they are fed, cabbage leaves seem to contain too little to be detected chemically. One is left with the possibilities that cabbage goiter is due either to iodine deficiency alone, to iodine deficiency exaggerated by the presence of thiocyanate, or to iodine deficiency plus a small amount of antithyroid compound of the thioöxazolidone type. It is of course possible that some batches of cabbage

may contain this compound; if this were the case, the erratic results of cabbage feeding, cited above, might be explained.

Rape seed goiter, on the other hand, seems clearly to be attributable to the seeds' content of the newly isolated compound. This compound could also be considered responsible for the goiter of sheep fed on turnips [16] and for the recent epidemic of goiter in western Europe among the peoples who had to subsist largely on brassica vegetables. [48]

There is good evidence that mustard seeds, either heated or not, are goitrogenic in rats, [16] but thus far no active compound has been found in mustard. The apparent goitrogenicity of peanuts, soya bean, [14] radish, [18] carrot, and pear [44] cannot be attributed to the compound found in turnips; the possible presence of other antithyroid compounds in these foods deserves exploration.

Why Is Not the Goitrous Individual More Obviously Hypothyroid?

It has been argued that, if goiter is due to a compensatory attempt on the part of the gland to remedy deficient thyroid function, then hypothyroidism should more often be detectable in individuals with goiter. This line of reasoning presupposes that the enlarging thyroid fails entirely in its attempt to remedy the deficit. Actually, the efficiency of the enlarged vascular hyperplastic gland is doubtless increased many fold. This increased efficiency is readily perceived if one examines the consequences of iodine deficiency. Under normal circumstances the thyroid is presented with iodide ion in a concentration of roughly one microgram per 100 cubic centimeters of circulating plasma. The resting gland can then concentrate this ion 20- to 50-fold so that there can be available in the thyroid cell a concentration of 20 to 50 micrograms per cent of iodide, ready for synthesis into the precursors of thyroid hormone. Should there be a deficiency of dietary iodine, one might imagine that the circulating iodide might fall to very low levels, but one can calculate that a concentration of as little as one-one hundredth of a microgram per 100 cubic centimeters of plasma might still be enough to permit a normal rate of thyroid function if one considers the increased efficiency of the hyperplastic gland. It has been shown both in man [49] and in animals [32] that the iodide ion-concentrating mechanism is highly efficient in the hyperplastic gland; such a gland can maintain an iodide ion concentration some 200 to 500 times that of the circulating blood. Now, if one adds to this 10-fold increase in efficiency for collecting iodide ion the increased rate of blood flow per unit of thyroid mass and the increase in total thyroid size, it is not inconceivable that a large hyperplastic goiter may be 100 times as efficient as a normal gland in collecting iodide from the blood. It is also known that the rate of organic binding of iodine is much more rapid in a hyperplastic gland (provided, of course, that this step is not specifically inhibited by an antithyroid compound), and this accelerated utilization of iodide ion could be a further factor in increasing the efficiency of the gland. The conclusion is

inescapable that compensatory hypertrophy and hyperplasia accomplishes its purpose and makes it possible for the thyroid to function normally in the face of drastic reductions in iodine intake.

The situation obtaining when a goiter is due to the administration of an antithyroid compound is more difficult to visualize. It would seem, however, that inhibition of this type poses a much more difficult problem for the thyroid gland. The increased iodide-concentrating capacity does little good, for the inhibition is beyond this step. Probably the increased capacity to bind iodine helps some, and it is likely that the effect of a submaximal dosage of an antithyroid compound could be completely or nearly completely countered by a sufficient degree of compensatory hyperplasia. If this be true, one should expect that the prolonged ingestion of small amounts of antithyroid substances would eventuate in goiter without myxedema. It is known, however, that full doses of an antithyroid compound given continuously to a normal individual causes both myxedema and goiter, and these two phenomena may appear almost simultaneously. Under these circumstances the goiter is the consequence of a wholly futile attempt at compensation.

The importance of the compensatory increase in the capacity of hyperplastic goiters to concentrate iodide ion is well illustrated by the effect of thiocyanate ion upon it. When the iodine intake is moderately reduced, myxedema, in association with thyroid enlargement, follows the administration of thiocyanate. This suggests again that the thyroid can make up for a low level of blood iodide by means of its special iodide-concentrating mechanism, but, when this is poisoned by the thiocyanate ion, the gland can no longer compensate and myxedema results.

This line of thought leads to the conclusion that the development of a goiter is an efficient means of counterbalancing an iodine deficiency. Compensatory hyperplasia is less effective in combating iodine deficiency when thiocyanate is present, and it may fail completely to make up for the defect in hormone synthesis induced by antithyroid compounds. As a corollary of this conclusion one might reasonably suspect that, when goiter is associated with myxedema or cretinism, the goitrogenic factor is either an extreme iodine deficiency or a positive influence, such as thiocyanate or an antithyroid compound. When goiter is unassociated with signs of hypothyroidism, iodine deficiency would be the most likely cause with a mild antithyroid influence a second, less probable, possibility.

A somewhat different conclusion would be reached if one considered the effects of treatment. Iodine deficiency goiter and that due to thiocyanate are readily prevented or reversed by added iodine while the only effective remedy for goiter due to an antithyroid compound is thyroid hormone itself. Though exact clinical data on the relative effectiveness of iodine and thyroid in the treatment of goiter are not available, many observers who have used thyroid since it was first introduced for this purpose in 1894 by Reinhold have found it a more certain remedy than iodine. Several extensive clinical experiments on the prevention of endemic goiter by increasing the iodine

intake clearly establish the effectiveness of this measure; the incidence of goiter is strikingly reduced, but goiter is by no means completely abolished by this procedure. This might suggest that some other factor besides iodine deficiency is contributing to goitrogenesis. The data cited above suggest that one of these other causes is to be found in the diet.

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CLINICAL ANGIOCARDIOGRAPHY: A CRITICAL ANALYSIS OF THE INDICATIONS AND FINDINGS *

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ANGIOCARDIOGRAPHY is that branch of clinical radiology which deals with the roentgenographic visualization of the thoracic cardiovascular structures during their opacification by intravenously injected radiopaque substances. Although significant preliminary investigations along similar lines of approach had been made by Forssman,[1] Egas Moniz, Carvalho, and Lima,[2] Conte, and Costa,[3] and Castellanos, Pereiras, and Garcia,[4] the work of Robb and Steinberg [5] in 1938 first established a practical method for the contrast visualization of the right and left cardiac chambers and great blood vessels. The technic of injection is still generally employed in its original form. During the intervening 11 years, many modifications have been devised and employed to afford serial records of the cardiovascular structures during their successive opacification following the angiocardiographic injection. Cineroentgenography, multiple cassette changers and automatic photoroentgen methods have been employed with success.[6, 7, 8] Perhaps the ideal device for angiocardiographic recording would be one which allowed the making of serial, direct, high-quality teleoroentgenograms of the chest at rapid intervals with short electrocardiographically controlled exposures. Simultaneous films in two projections would give a two dimensional study with a single injection and permit volumetric determinations of cardiac chambers and vessels. The possibilities of such apparatus are being explored at present; equipment fulfilling the above criteria is under construction.

Elaborate apparatus of this nature will find its fullest use in larger centers only, however, and will be out of the practical range of many clinicians. For the hospital roentgenologist or clinician of more modest means, the method as originally described by Robb and Steinberg will suffice to make satisfactory diagnostic films. This statement is made following an 11 year experience with the method, during which time over a thousand patients were studied without fatality. The vast majority of these examinations were conducted in the manner originally reported and all the illustrations in this study demonstrate the diagnostic adequacy of the method.

During the past 18 months, the use of Neo-Iopax, 75 per cent (sodium iodomethamate) in angiocardiography has been studied. Four hundred

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and forty-eight have been made in 305 patients. Dosage varied from 15 c.c. in infants to 45 c.c. in adults and an occasional patient received as many as three 45 c.c. injections within an hour's time. Contrast visualization afforded by this compound has been comparable to that obtained with Diodrast, 70 per cent (diiodopyridone acetic acid diethanolamine). There have been no serious reactions. The usual reaction consists of a feeling of mild heat starting in the chest and neck and spreading throughout the body, followed at about 30 to 45 seconds after the injection by a throbbing frontal headache of negligible to considerable severity. This is apparently associated with a mild elevation of blood pressure and subsides spontaneously in five to 10 minutes. Weakness, flush, pallor and thirst are often noted. During filling of the pulmonary capillary bed, a tendency to cough is occasionally observed which can usually be controlled by the patient. In six instances transient arm pain was noted. This was usually associated with stenotic lesions of the subclavian and innominate veins or the superior vena cava and is thought to represent local venous spasm. Urticaria or angioneurotic edema has not been observed and it has not been necessary to employ epinephrine. Save for chemical thrombosis of the injected vein in an estimated 30 to 40 per cent of the cases, there have been no late reactions. Neo-Iopax, 75 per cent, in our hands has proved to be a satisfactory medium for angiocardiography. The as yet unrealized ideal contrast substance for angiocardiography would produce neither reactions nor side effects and would afford greater contrast with a much smaller injected volume.

In the 11 year period following the introduction of angiocardiography, the method has proved to be of definite diagnostic value in a variety of disorders which manifest themselves in disturbed cardiovascular relationships within the thorax. In revealing the anatomy of the cardiac chambers and in delineating clearly the form of previously indistinguishable structures, angiocardiography has immeasurably added to the precision and adequacy of roentgenologic diagnosis. Although valuable physiological data have been gained through contrast cardiovascular visualization, the chief value and direction of approach of angiocardiography have been anatomical. Angiocardiography has been of particular value in the definitive diagnosis of certain abnormal states; the findings in these conditions will be briefly described.

Congenital Heart Disease

The combined facilities of angiocardiography and cardiac catheterization have made possible the accurate diagnosis of the vast majority of congenital cardiac anomalies during life. The development and widespread application of surgical methods for the treatment of congenital heart disease has taken the problem of diagnosis in this condition out of the hands of the academic few and placed it into the hands of the medical profession at large. Fortunately, neither angiocardiography nor cardiac catheterization is a difficult procedure to master in terms of technic and interpretation. The clinical ap-

plication of angiocardiography to the more common congenital defects will be summarized and illustrated.

Coarctation of the Aorta (figure 1). Angiocardiography, in adequately demonstrating the exact, measurable anatomical features of coarctation of the aorta is indispensable in the preoperative study of this condition. The most

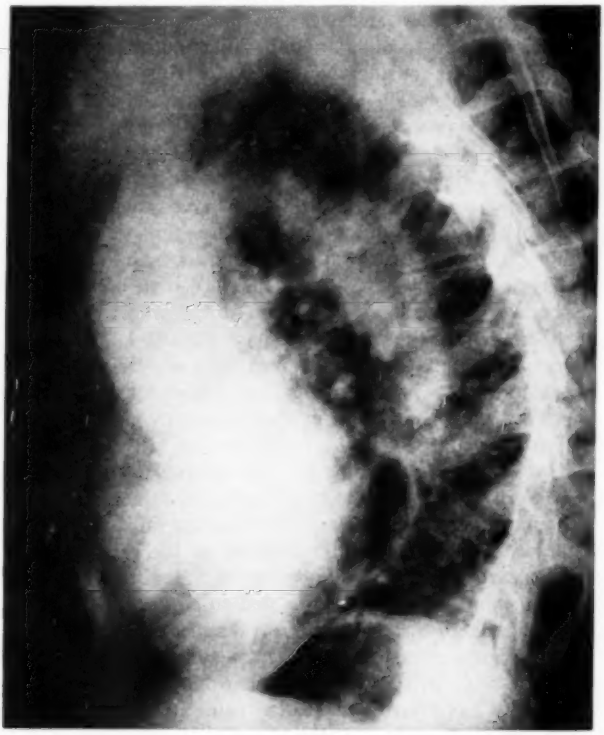

FIG. 1. *Coarctation of the Aorta.* Male, 54. Recurrent cardiac failure for six years. Classical physical and roentgen signs of coarctation of aorta. Blood pressure in arms 170/80; in legs 110/49. Rib notching present. *Left anterior oblique angiocardiogram.* Aorta opacified. Note coarctation 2.5 cm. distal to origin of left subclavian artery. Dilated ascending aorta is seen, as are prominent internal mammary arteries anastomosing with superior epigastric arteries.

adequate angiocardiographic demonstration of coarctation of the aorta is obtained in the left anterior oblique projection. The ascending aorta usually is seen to be dilated and gives rise to large brachiocephalic arteries. Markedly dilated internal mammary arteries often are seen paralleling the sternum and anastomosing with the superior epigastric arteries below. The actual site of coarctation is usually seen as a narrowing slightly distal to the site of

origin of the left subclavian artery. Generally the descending aorta fills with contrast substance and is dilated for a short distance just beyond the point of narrowing. Less frequently the site of coarctation is seen to be proximal to the origin of the left subclavian artery, a condition loosely referred to as the "infantile" type of coarctation.

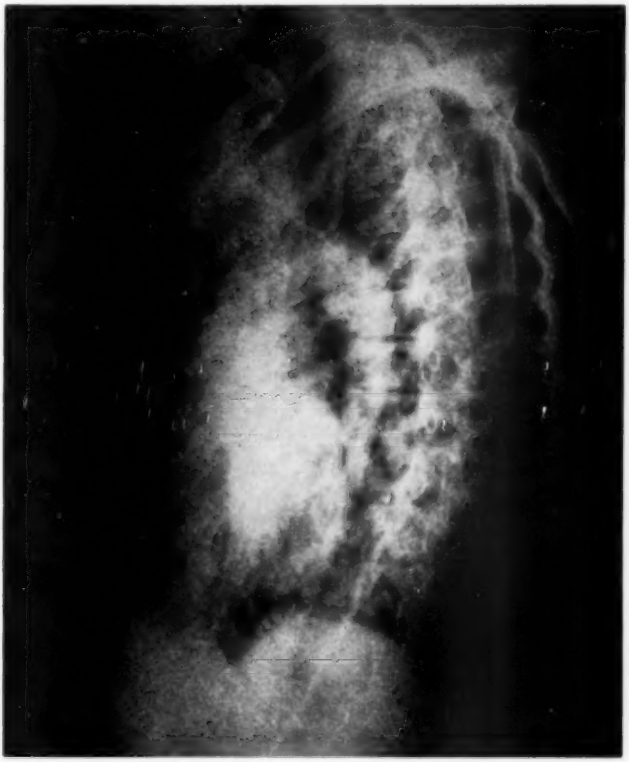

FIG. 2. *Patent Ductus Arteriosus.* Female, 27. Characteristic to-and-fro murmur was present. *Left anterior oblique angiocardiogram.* Note the dilatation of the aorta just beyond the site of origin of the left subclavian artery, an inconstant sign of patent ductus arteriosus. Diagnosis confirmed at surgical obliteration.

Patent Ductus Arteriosus (figure 2). The diagnosis of patent ductus arteriosus is best made by physical examination and confirmed by cardiac catheterization. Angiocardiography in this condition regularly demonstrates elevation and enlargement of the left pulmonary artery, and often reveals a dilatation of the aorta at the site of origin of the ductus. [9] This dilatation has been observed in two cases (of mediastinal tumor) which on

subsequent thoracotomy were shown to have neither demonstrable ductus arteriosus nor ligamentum arteriosum. In addition, the dilatation has been absent in an instance of patent ductus arteriosus proved at surgical ligation, and therefore cannot be considered to represent reliable evidence for or against patent ductus arteriosus. Reopacification of the left branch of the pulmonary artery is occasionally observed in this condition, and actual opaci-

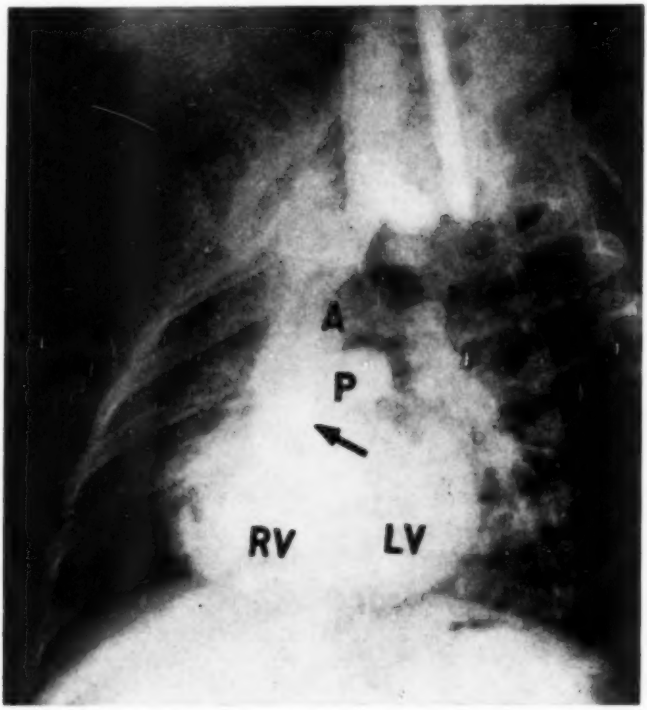

FIG. 3. *Tetralogy of Fallot.* Female, 4. Cyanosis, dyspnea since one and one-half years. Loud systolic murmur in pulmonic area. *Left anterior oblique angiocardiogram at two seconds.* Note simultaneous opacification of aorta and pulmonary artery, stenosis of pulmonary conus and enlargement of the right ventricle. Findings confirmed at Blalock-Taussig operation.

fication of the ductus itself has been observed in two instances. Retrograde injection of the left common carotid artery with contrast substance affords far better visualization in patent ductus arteriosus than does angiocardiography although it is a more difficult and perhaps a less safe procedure.

Tetralogy of Fallot (figure 3). In the diagnosis of cyanotic congenital heart disease with pulmonic stenosis, angiocardiography has been of considerable value. By angiocardiographic means, the differential diagnosis be-

tween tetralogy of Fallot and transposition of the great blood vessels, Eisenmenger's syndrome, and common truncus arteriosus may be facilitated. The surgical implications of pre-operative demonstration of the anatomy in such conditions are obvious. The various features of the usual tetralogy of Fallot are usually well seen in a left anterior oblique film made two seconds after the beginning of the injection. These signs include: (1) simultaneous opacification of the aorta and the pulmonary artery, (2) simultaneous opacification of a large right and a small left ventricle, (3) an area of stenosis in the pulmonary conus or artery and (usually) a small, poorly filled pulmonary arterial tree.

Congenital Aneurysm of the Pulmonary Artery and Isolated Pulmonic Stenosis (figure 4). Angiocardiography affords a method for classifying the various causes of dilatation of the pulmonary artery. [11] The diagnosis of congenital aneurysm of the pulmonary artery, although it cannot be made exclusively by this means, should include angiocardiographic visualization of the abnormally dilated vessel. [12] This is best afforded in the true lateral view which not only reveals the dilatation but also rules out the presence of pulmonic stenosis, a possible cause of pulmonary artery dilatation in the adult. In both conditions valuable diagnostic data are afforded by both the anatomic studies of angiocardiography and the dynamic information afforded by intrapulmonary artery pressure studies. The exact degree and site of isolated pulmonic stenosis as well as the often encountered post-stenotic pulmonary artery dilatation may be angiocardiographically shown and are best demonstrated in the lateral view.

Septal Defects (figure 5). In the interest of accurate diagnosis of congenital anomalies, it is often desirable to establish the presence and site of intracardiac shunts. The angiocardiographic diagnosis of defects in the intra-cardiac septa has been somewhat disappointing. It is regularly possible to demonstrate chamber and vascular enlargement associated with interatrial or inter-ventricular septal defects, but it has been possible in only a small percentage (about 30 per cent) of suspected cases to demonstrate either right to left trans-septal spread of the contrast substance or re-opacification of the right heart chambers at the time of left heart filling. A few notable and convincing exceptions to the contrary have been observed, but in general, the diagnosis of septal defect is far better made by cardiac catheterization studies. In this connection we are at present developing a method whereby we hope not only clearly to outline defects in the atrial septum, but to afford exact measurement of their size.

Anomalous Pulmonary Veins (figure 6). With the advent of angiocardiography the diagnosis of pulmonary veins draining into the right heart may for the first time be made during life. Although at present primarily of academic interest, this diagnosis assumes increased importance. Andrus [13] has suggested the possibility of surgical implantation of the anomalous vein into the left atrium. In the presence of such an anomaly, angiocardiograms

timed to show filling of the left atrium also reveal the filling of an abnormal vessel draining blood from some part of the lung and emptying into the right atrium or its tributaries.[14]

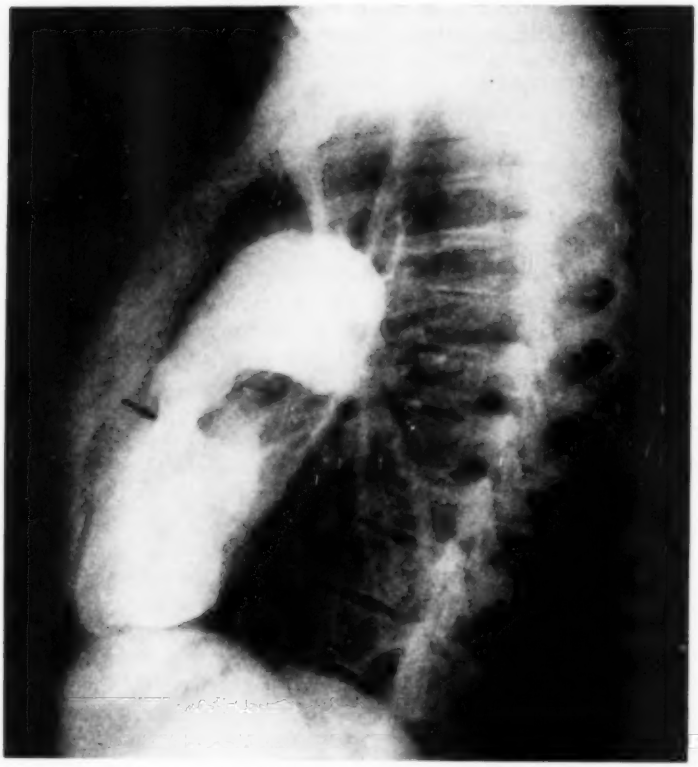

FIG. 4. *Isolated Pulmonic Stenosis.* Female, 23. Asymptomatic. Loud, rough, high pitched systolic murmur in pulmonic area with thrill. *Left lateral angiocardiogram.* Arrow indicates point of stenosis in pulmonary conus below pulmonic valves. Note dilatation of mainstem pulmonary artery and branches distal to stenosis. There was no evidence of associated congenital defects.

ACQUIRED HEART DISEASE

Many diagnostic problems related to acquired heart disease have benefited by angiocardiographic study, notably the diagnosis of syphilitic aortitis, the differentiation of aneurysm from mediastinal tumor and the diagnosis of pericardial effusion.

Hypertension (figure 7). Angiocardiography permits complete visualization of the unfolded aorta but otherwise adds little information to that

afforded by conventional clinical and roentgenologic methods in the diagnosis of uncomplicated hypertension. The angiocardiographic findings in hypertension consist of the demonstration of left ventricular chamber enlargement, dilatation of the ascending aorta and unfolding of the aortic arch. These changes are best seen in the left anterior oblique view. The aorta in hyper-

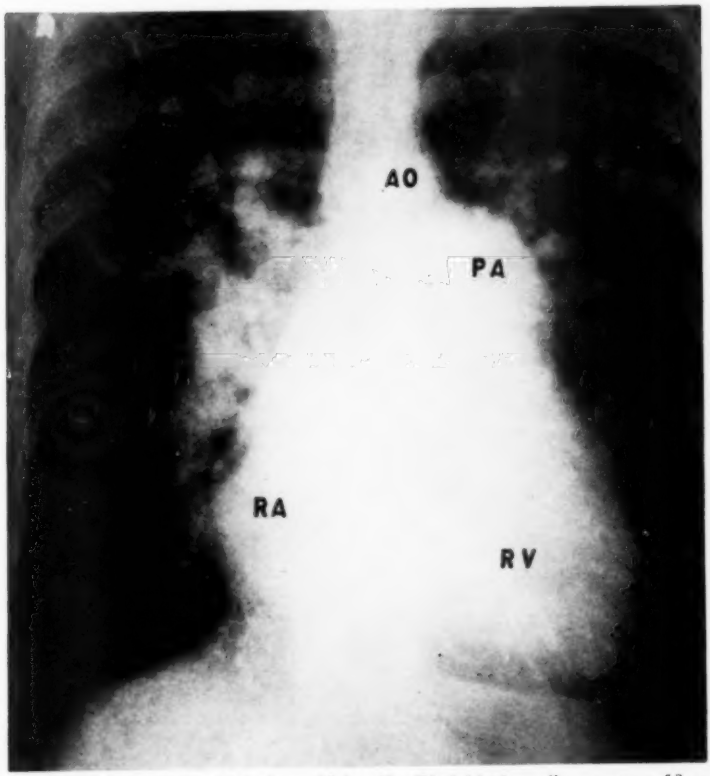

FIG. 5. *Interatrial Septal Defect.* Male, 42. Diminished cardiac reserve, 12 years. Loud systolic murmur along left sternal border and "hilar dance" on roentgenoscopy. *Frontal angiocardiogram at eight seconds.* Note opacification of small aorta (AO), reopacification of right atrium (RA), right ventricle (RV) and tremendously dilated pulmonary artery and branches. Diagnosis confirmed by cardiac catheterization (superior vena caval blood: 7.6 vol. per cent oxygen, right atrial blood 15.4 vol. per cent oxygen).

tension may vary in size between the normal mid-ascending caliber (average, 28 mm.; upper limit, 38 mm.) to moderate dilatation (up to 46 mm. in our series). In contrast to the changes in syphilis, the dilatation is even and the lumen is customarily smooth in contour. The aortic wall is normal in thickness (2 to 3 mm.). There has as yet appeared to be no fixed correla-

tion between the duration and degree of hypertension and the amount of aortic dilatation.

Arteriosclerotic Heart Disease (figure 8). Aside from demonstrating the distorted course of the elongated aorta in the presence of arteriosclerotic changes and thereby differentiating it from aneurysm or tumor, angiocardiography has been of little value in arteriosclerotic heart disease. It is occa-

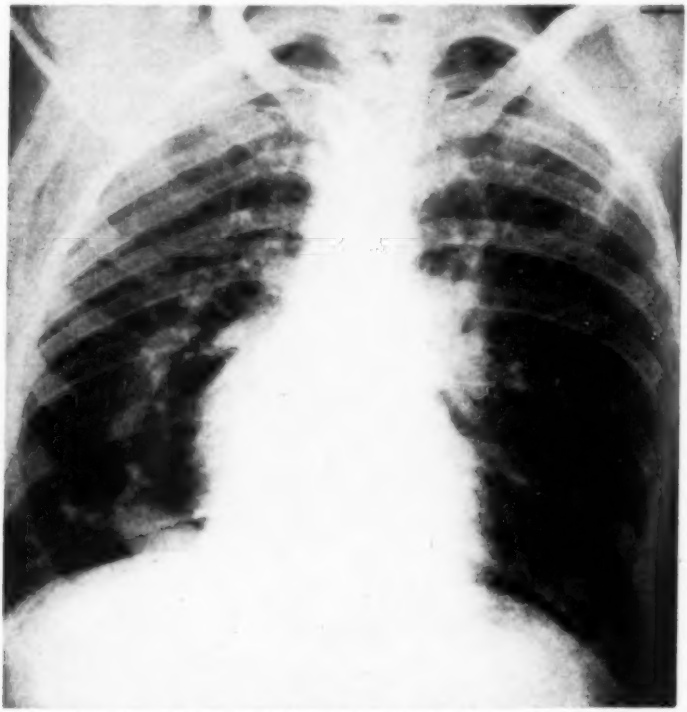

FIG. 6. *Anomalous Pulmonary Vein Entering Inferior Vena Cava.* Male, 27. Asymptomatic. Crescent-like shadow, right lower lung field found on routine chest roentgenogram. *Frontal angiocardiogram at 8.5 seconds.* Note filling of left heart, pulmonary veins and aorta and simultaneous opacification of a vascular trunk draining blood from the right lung to a point below the diaphragm.

sionally difficult to distinguish between arteriosclerotic aortic elongation of the aorta and tumor or aneurysm, a distinction made with ease by angiocardiographic means. [15] Arteriosclerotic plaques may rarely be visualized as localized areas of thickening of the aortic wall. Because of the increased denseness of the aortic wall in arteriosclerosis, angiocardiograms of the atherosclerotic aorta frequently show strikingly sharp contrast.

Rheumatic Heart Disease (figure 9). Aside from its academic interest,

angiocardiography is of little value in rheumatic heart disease wherein physical examination and conventional roentgenography are generally diagnostically sufficient. Exceptions to this lie in the differential diagnosis between marked cardiac enlargement and pericardial effusion and in the occasional demonstration of thrombi within the cardiac chambers in the presence of auricular fibrillation. Angiocardiographic study of the heart has excluded

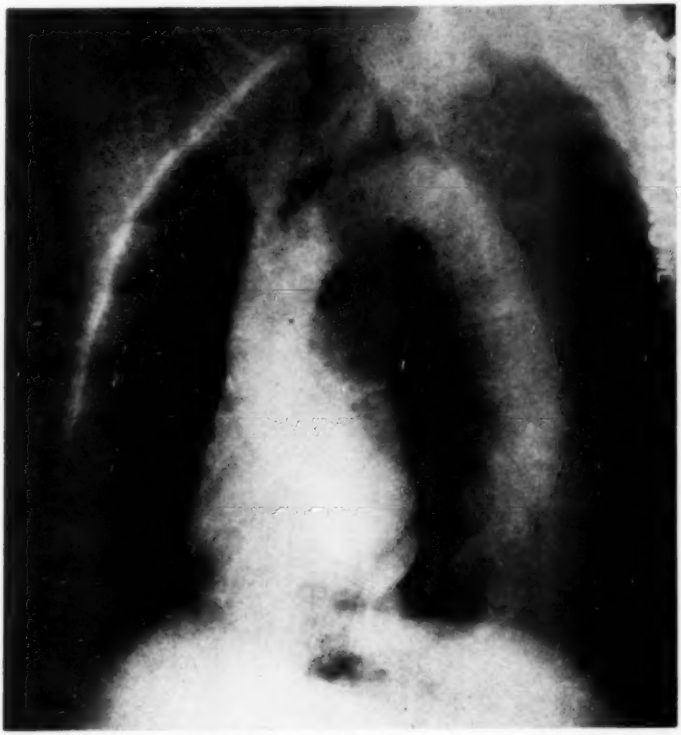

FIG. 7. *Hypertensive Heart Disease.* Male, 68. Blood pressure 180/110. No apparent decompensation. *Left anterior oblique angiocardiogram.* Left ventricle enlarged. Note elongated, moderately dilated thoracic aorta.

the term "pulmonary conus" from an accurate description of the frontal roentgenogram in mitral stenosis. The prominence in the left mid-cardiac border in this condition has been repeatedly shown to consist of (1) an enlarged, elongated main-stem pulmonary artery and its left branch and (2) the left auricular appendage. The earliest angiocardiographically observed change in mitral stenosis has consisted of enlargement of the left atrium. This is well demonstrated in the left anterior oblique view, timed to show

filling of the right heart, and with the esophagus outlined by barium swallow. The posterior deviation of the esophagus and the anterior impression on the right atrium thus outline in negative relief the enlarged left atrium. This can be borne out in films made to show left atrial filling.

Pericardial Effusion (figure 10). The diagnosis of fluid within the pericardial space occasionally presents considerable clinical difficulty but is made with ease and certainty by angiocardiography. Films timed to show right

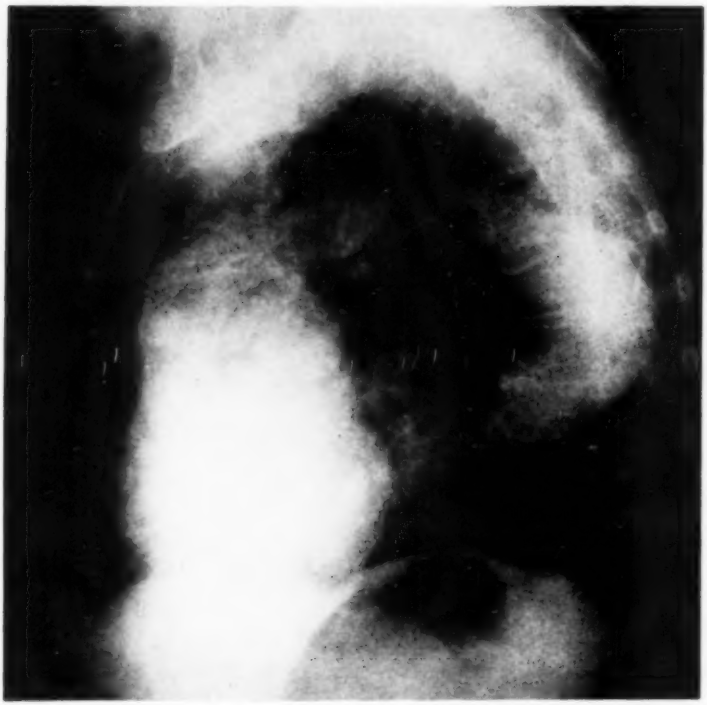

FIG. 8. *Arteriosclerosis of Aorta.* Male, 69. Previous myocardial infarction. Peripheral arteries markedly sclerotic. *Left anterior oblique angiocardiogram.* Note sharply opacified, markedly elongated, tortuous thoracic aorta.

atrial opacification demonstrate the presence of an increased non-opacified area between the right atrium and the right lung field. Normally this distance represents the thickness of the wall of the right atrium and measures (as seen angiocardiographically) not above 2 to 4 mm. Visualization of the left ventricular cavity in the presence of pericardial effusion shows its outer border to be well within the left margin of the cardiac shadow, thereby demonstrating the presence of fluid on the left side. Angiocardiography affords

virtually as conclusive proof of the existence of pericardial effusion as does pericardial tap, is more easily performed and is probably much safer. [16]

Syphilitic Aortitis and Aneurysm (figure 11). The angiocardiographic diagnosis of uncomplicated syphilitic aortitis represents a definite contribution toward the early detection of cardiovascular syphilis. [17, 18] The angiocardiographic signs of syphilitic aortitis are abnormal dilatation of the as-

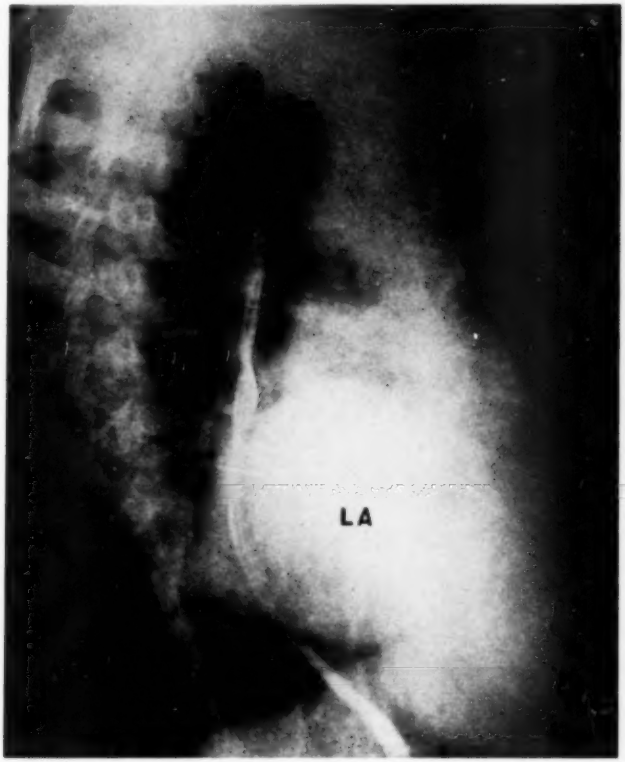

FIG. 9. *Rheumatic Mitral Stenosis.* Male, 49. Rheumatic mitral stenosis for seven years with recent cardiac failure. Typical diastolic rumble was present. *Right anterior oblique angiocardiogram at 16 seconds.* Note opacified, markedly dilated left atrium displacing barium filled esophagus posteriorly.

cending aorta (above 38 mm., caliber), as measured in the left anterior oblique projection; irregularity of the aortic lumen; variations in aortic wall thickness, and aortic aneurysm. Dilatation, the most significant evidence of the early changes in syphilitic aortitis, must be evaluated with care since it may also be caused by hypertension, non-syphilitic aortic insufficiency, and by congenital anomalies of the aortic arch. In our experience, arterioscler-

otic changes alone rarely if ever produce significant dilatation of the ascending aorta. In this connection, the standards for aortic measurement were established by the study of films made at a six-foot tube-screen distance; figures derived from angiocardiograms made at less than that distance will be falsely higher and therefore not comparable.[19]

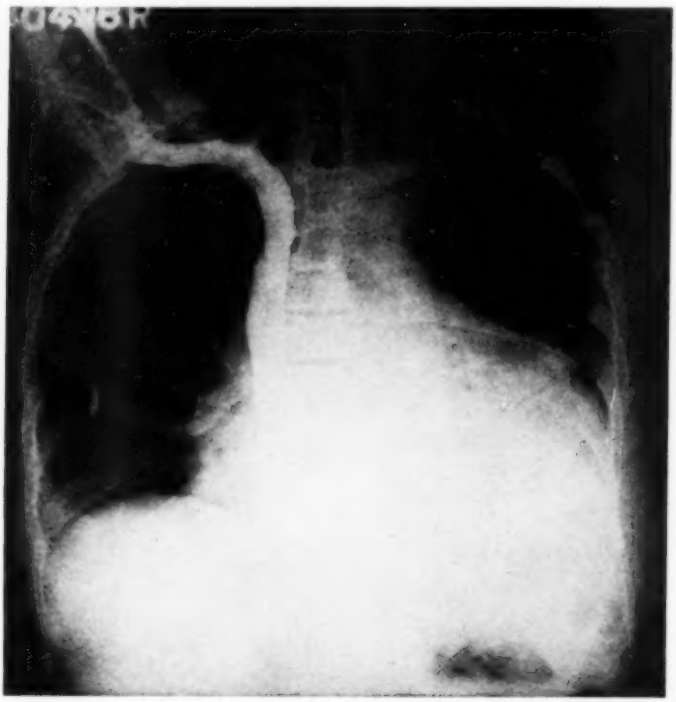

FIG. 10. *Pericardial Effusion.* Female, 56. Dyspnea three years. Large heart without physical or electrocardiographic evidence of pericardial fluid. *Frontal angiocardiogram.* The wide interval between the opacified right atrium and the right heart border made possible the angiocardiographic diagnosis of pericardial effusion. Diagnosis confirmed by pericardial tap when 400 c.c. of fluid were removed. Etiology of the effusion was never established.

The diagnosis and delineation of aortic aneurysm has been made a simple process by angiocardiography. Previously inaccessible sites of aortic dilatation such as the sinuses of Valsalva may now be clearly outlined. The rare instances of clotted aneurysms which do not fill with contrast substance are usually recognized by the demonstration of collateral evidences of syphilitic aortic disease. Angiocardiography cannot be relied upon to distinguish between syphilitic and congenital aneurysms of the aortic arch and clinical judgment must be the eventual deciding factor when this possibility arises. [20]

Dissecting Aneurysm. The changes of dissecting aneurysm of the aorta as seen angiocardiographically are distinctive. The aortic lumen is seen to be more or less abruptly narrowed and the aortic walls thickened at the site of the dissection. Contrast substance has been angiocardiographically demonstrated within false passageways formed by dissecting aneurysms.[21]

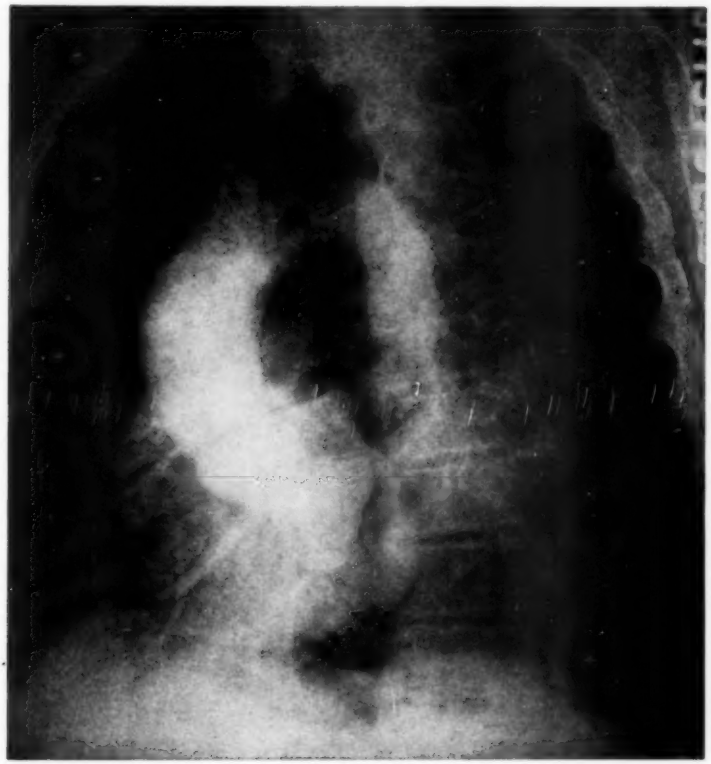

FIG. 11. *Syphilitic Aortitis.* Male, 56. Late, untreated syphilis. Blood pressure 135/75. Clinical diagnosis of possible syphilitic aortitis based upon aortic systolic murmur. *Left anterior oblique angiocardiogram.* Note opacification of irregularly dilated ascending aorta which measured 42 mm. in caliber.

Pulmonary Heart Disease (figure 12). Although the diagnosis of pulmonary heart disease is best arrived at by studies of cardiac and pulmonary function, early morphologic changes may frequently be demonstrated by angiocardiography. Left anterior oblique angiocardiograms reveal enlargement of the right ventricle, while lateral and frontal films reveal enlargement of the pulmonary artery and its branches. Elongation, followed by dilata-

tion of the pulmonary artery are early changes in pulmonary heart disease. These probably occur concomitantly with right ventricular hypertrophy and elongation of the pulmonary conus. In all probability the earliest demonstrable abnormalities in pulmonary heart disease are physiological rather than anatomical, as far as the cardiovascular system is concerned. [11]

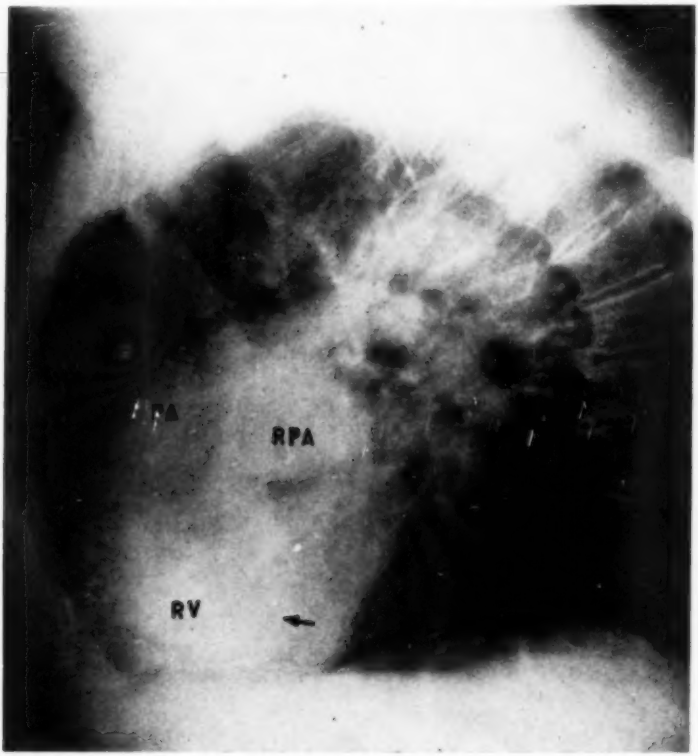

FIG. 12. *Cor Pulmonale.* Male, 71. Dyspnea, cough for many years. Physical and roentgen examination revealed marked pulmonary emphysema. *Left lateral angiocardiogram.* Note opacification of markedly enlarged right atrium, right ventricle (RV), pulmonary artery (PA) and its branches. Right pulmonary artery (RPA) is seen end-on. Arrow indicates interventricular septum.

Constrictive Pericarditis (figure 13). The operative relief afforded patients with constrictive pericarditis has long been recognized, and complete study in this condition is therefore of more than academic value. Although angiocardiography is unnecessary in making the diagnosis, [22] it adds otherwise unobtainable information to the study of individual cases. The angiocardiographic findings in constrictive pericarditis vary among cases, but usu-

ally include the demonstration of a grossly dilated superior vena cava merging imperceptibly into a dilated right atrium. The ventricular cavities are usually found to be normal or reduced in size, as would be anticipated. The thickness of the ventricular wall plus the thickened pericardium may often be demonstrated, and contrast studies aid in the localization of pericardial or myocardial calcifications.

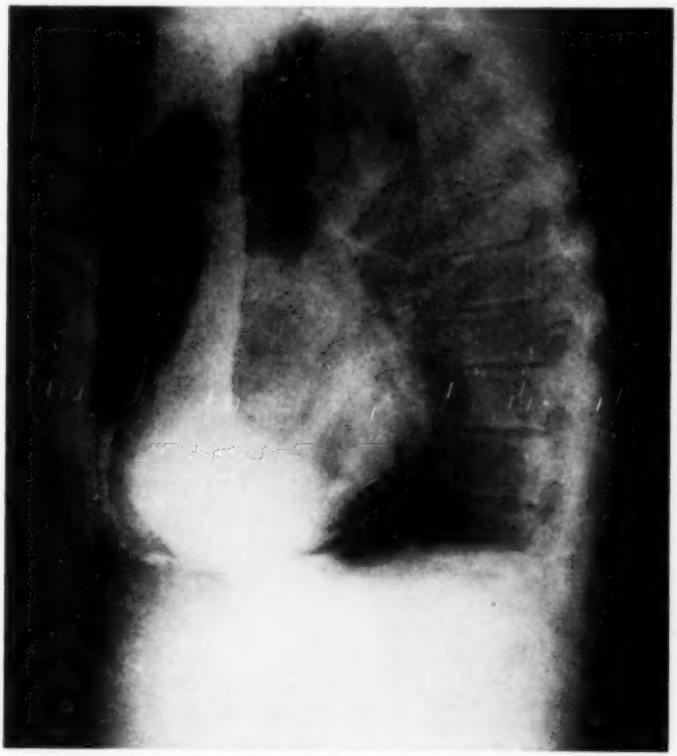

FIG. 13. *Constrictive Pericarditis.* Male, 49. Ascites, dependent edema and dyspnea, two years. Markedly elevated venous pressure, paradoxical pulse. Calcification of pericardium seen on conventional roentgenogram. *Left anterior oblique angiocardiogram at two seconds.* Note opacification of dilated superior vena cava and right atrium. The right ventricular wall appears thick and contains or is surrounded by calcification.

MEDIASTINAL TUMORS

Contrast visualization of the cardiovascular structures in the pre-operative investigation of mediastinal tumors affords otherwise unobtainable diagnostic and prognostic information. Angiocardiography, by outlining cardiovascular structures in contact with the inner or "hidden" margins of

mediastinal tumors, serves to delimit and more accurately localize the mass within the mediastinum as well as rule out the presence of aneurysm. Further evidence of a differential nature is gained by the demonstration of the effect of a tumor upon the thoracic great blood vessels. Thus, while a dermoid cyst may be seen to displace major vessels, a malignant thymoma

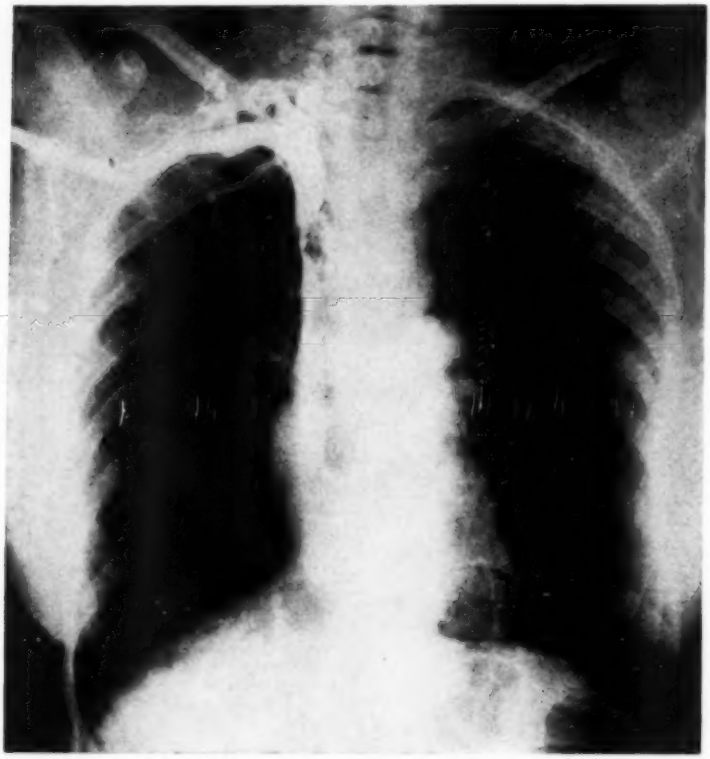

FIG. 14. *Malignant Mediastinal Tumor.* Female, 38. Edema and cyanosis of face, neck, arms and chest for four months. Venous pressure in arms 300. *Frontal angiocardiogram at two seconds.* Note multiple filling defects of superior vena cava and extensive venous collateral channels. Biopsy of anterior chest wall lesion one year later showed carcinoma, primary site unknown.

or teratoma shows a tendency to cause stenotic or obstructive changes. By demonstrating to the surgeon the structures bounding a mass to be extirpated, angiocardiography aids in planning operative attack.[23]

Benign Mediastinal Tumors. Bronchiogenic, dermoid or pericardial cysts are usually demonstrable angiocardiographically as single masses causing a variable degree of displacement of the great blood vessels or cardiac

chambers, but not producing significant obstruction to vessels. The study of such tumors should include two injections in positions at right angles to each other so as to give maximum three dimensional information of use in formulating surgical measures.

Malignant Mediastinal Tumors (figure 14). Contrast studies in the presence of lymphomata of the mediastinum are chiefly of value in two ways: (1) multiplicity of lesions, a diagnostic feature, may be demonstrated, (2) vascular involvement such as superior vena caval obstruction, may be shown. These features may aid in arriving at a decision as to the choice between radiation therapy and surgical approach. The angiocardiographic positions employed to study these as any tumors of the chest must be selected upon the basis of the location, size and shape of the mass or masses in question, and by the clinical findings. Thus in a patient suspected of having a right innominate vein obstruction, the position of choice would be the frontal position and the injection would be made in the right arm. Other malignant mediastinal tumors, both primary and metastatic, manifest equally a tendency toward stenosis and obstruction of great blood vessels.

Bronchogenic Carcinoma (Figure 15)

The angiocardiographic findings in bronchogenic carcinoma are those of malignant tumors in general, often have both diagnostic and prognostic application and aid in formulating surgical measures. Stenosis and occlusion of major pulmonary arteries at or near the hilar areas constitute evidence in favor of a malignant neoplastic process, although it must be borne in mind that non-malignant tumors or infectious and granulomatous hilar lymph node enlargement may by external pressure cause changes in the caliber and configuration of pulmonary vessels. As in barium study of the gastrointestinal tract, however, the distinction between extrinsic pressure defects and the changes produced by neoplastic infiltration may usually be recognized. It is frequently possible, by virtue of the demonstration of malignant involvement of central vascular structures, to arrive at an operative prognosis in a given instance of lung cancer. Sufficient experience has not been accumulated to deny the patient with bronchogenic carcinoma the possible aid of surgical intervention on the basis of angiocardiographic evidence of inoperability. The projection of choice for the angiocardiographic study of lung cancer is the frontal projection since this affords the best view of the pulmonary vessels and of the hilar and mediastinal structures.

Chronic Pulmonary Disease

Both anatomical and dynamic changes in the vascular supply to affected portions of the lungs may be shown by contrast visualization in the presence of various chronic pulmonary disorders. In tuberculosis a relative hypovascularity is seen, and in the presence of long-standing disease, there is seen distortion and displacement of the pulmonary vessels which is incident upon fibrosis and cicatricial changes. Bronchiectasis is often associated with ap-

parent poor filling of the pulmonary arteries supplying the affected lobes, while in pulmonary emphysema, and particularly the localized bullous type, the separation of pulmonary artery radicles by emphysematous areas of lung parenchyma is often striking. In the presence of atelectasis, filling of the vessels to the collapsed area of lung is poor, and these vessels are seen to be

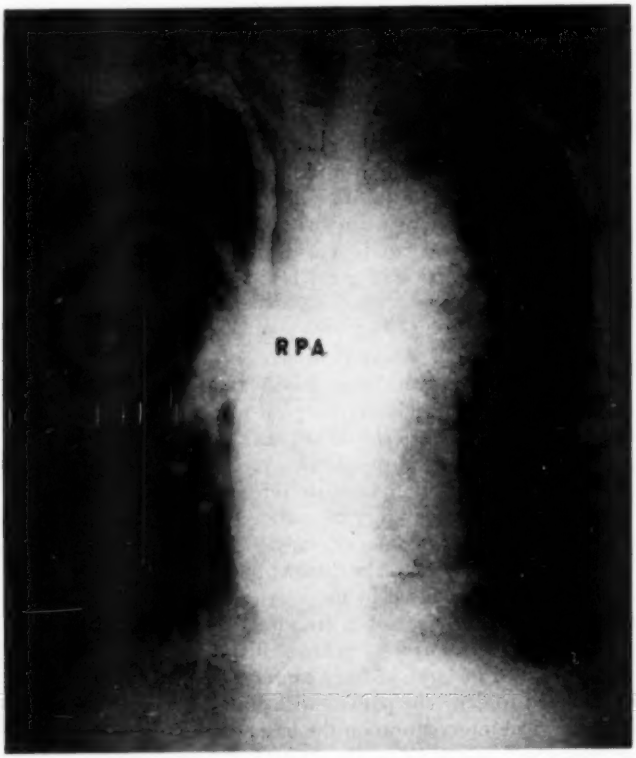

FIG. 15. *Bronchogenic Carcinoma.* Male, 51. Weight loss, cough, dyspnea and left chest pain for a year. *Frontal angiocardiogram.* Note complete occlusion of left pulmonary artery by tumor in left upper lung field. The opacified right pulmonary artery (RPA) is dilated. Exploratory operation confirmed the findings.

crowded closely together, findings which aid in the more accurate identification and localization of areas of atelectasis. [24] Diminished vascularity is seen in the presence of pneumothorax. [25]

THORACIC DEFORMITY (FIGURE 16)

The displacement of heart and great blood vessels in kyphoscoliosis, thoracoplasty, pneumothorax, and following pneumonectomy and lobectomy

may be delineated with ease angiocardiographically, and certain physiological data may be obtained concerning cardiopulmonary function in such instances. Following pneumonectomy, or in the presence of a non-functioning lung, the increased circulation to the remaining or functioning lung is often indicated by the demonstration of an enlarged branch of the pulmonary artery supplying that side.

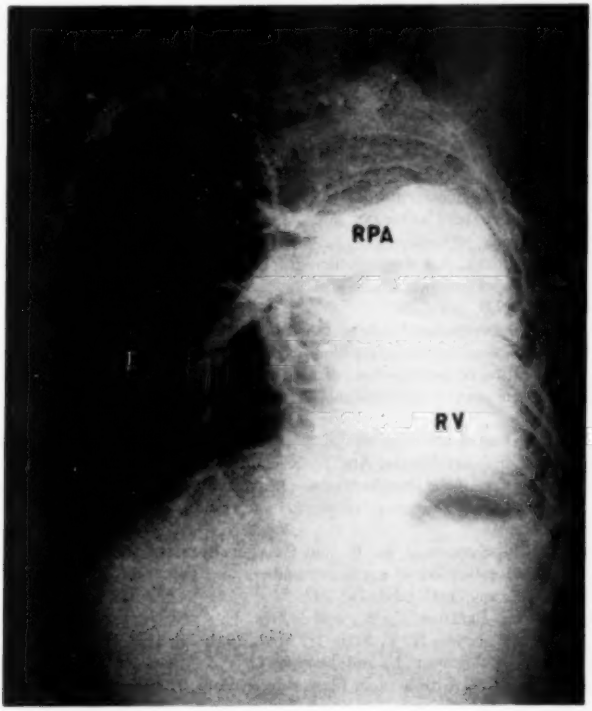

FIG. 16. *Pneumonectomy.* Female, 10. Pneumonectomy for extensive left lung bronchiectasis three years previously. *Frontal angiocardiogram.* Note pronounced rotation of heart and blood vessels into left chest. The right pulmonary artery is considerably enlarged.

SUMMARY AND CONCLUSIONS

During the past 11 years, the angiocardiographic study of over 1,000 patients has been conducted without fatality, thus indicating the safety of this diagnostic method. In the presence of certain pathological states, angiocardiography has emerged as an indispensable diagnostic technic. Contrast cardiovascular visualization has been shown to be of its greatest value in the diagnosis of the following conditions: Coarctation of the aorta; tetralogy of

Fallot and related lesions; isolated pulmonic stenosis; anomalous pulmonary veins; aneurysms, congenital and acquired; pericardial effusion; uncomplicated syphilitic aortitis; mediastinal tumors; bronchogenic carcinoma.

The understanding of various other abnormal conditions such as patent ductus arteriosus, septal defects, hypertensive, arteriosclerotic, rheumatic, and pulmonary heart disease as well as constrictive pericarditis and chronic pulmonary disease, has been enhanced by angiocardiographic study, although diagnosis in such conditions is usually made without resort to contrast visualization. An attempt has been made in this report briefly to summarize the significant angiocardiographic findings in the above clinical conditions, and to suggest the circumstances under which this method of examination is most productive.

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POLIOMYELITIS: EARLY DIAGNOSIS AND EARLY MANAGEMENT OF ACUTE CASES *

By JOHN R. PAUL, M.D., F.A.C.P., *New Haven, Connecticut*

THE title of this paper indicates that it will be concerned with early aspects of diagnosis and therapy. But the adjective *early* should be especially stressed, for, from the standpoint of the acute infection, the early and critical stage of poliomyelitis has heretofore been regarded clinically as the prodromal stage. By the time patients begin to show evidence of paralysis, and often by the time they reach the hospital, it may be late in the disease and the critical period is already passed. Thus according to Russell[1]: "the battle to decide the fate of the spinal-cord cells is probably over before paralysis is detected." There is some experimental evidence [2, 3] to bear this out; and according to Bodian [3] the virus reaches its maximum concentration in the spinal cord some 24 hours before paralysis is detectable, and as paralysis advances, the concentration of virus drops rapidly. We also have learned from the work of Hammon [4] and others, that by the time poliomyelitis patients are admitted to the hospital, the chances are that antibodies to the virus are already present in the blood stream, indicating that infection has been present somewhere in the body for some days.

Before reviewing the clinical picture in this light it may be well to point out that there are certain things about poliomyelitis which are apparently changing, both in respect to its clinical picture and its epidemiology. Primarily we face the fact that the age of the average poliomyelitis patient seen by clinicians in this country is apt to be older than was the case a generation ago. It is clear that the textbook [5] statement made at the turn of the century: "that the disease is rather rare after the age of six," no longer holds. Thus it has become apparent in Scandinavia and in this country, as well as in Canada, in some parts of Europe, and in Australia, that today most of the cases of poliomyelitis in any given epidemic are to be found in children of school age, and in adolescents. In this sense we no longer have "the infantile paralysis." There are certain obscurities about this situation, for, although the percentage of cases in the older age groups has shown a steady increase in consecutive series of cases from certain areas, the contemporary *age specific* rates do not always indicate that adolescent or adult *case rates* are increasing. [6, 7] Nevertheless the fact remains that the average series of poliomyelitis cases in succeeding epidemics within the U. S. contains a decreasing *percentage* of infants and an increasing *percentage* of people over

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15 years of age. No ready explanation for this shift in the behavior of the disease is available, other than it is in part due to shifts in the age composition of the populations involved. But regardless of the explanation, the implication is clear. We should turn our attention more to the clinical picture of *adult poliomyelitis*, now that it is becoming more common.

Another change is that the per cent of those cases which do not go on to lasting paralysis is apparently on the increase. This may be more apparent than real and actually due to the fact that the non-paralytic cases * have merely received more clinical attention than they did before. In any event, in the 1916 epidemic in New York City, *non-paralytic cases* amounted to about 13 per cent of the total cases [8]; whereas in 1935 in that same city, 33 per cent were recorded as having no paralysis. [9] More recently (1947) we have seen epidemics labelled as poliomyelitis in the middle Atlantic states, in which this percentage has gone up to 70 per cent or above, indicating that but a small fraction of the cases were paralytic.

Here again the explanation for this apparent increase in cases which do not go on to paralysis and yet are called poliomyelitis, is lacking. But regardless of the explanation it is clear that clinicians are called upon today to consider relatively more cases of non-paralytic poliomyelitis than did the preceding generation of physicians. Actually the increase in non-paralytic cases does not make the physician's task any easier in the earliest stages of the disease. For who can tell which cases will go on to paralysis,—in view of the fact that the early symptoms of abortive and non-paralytic poliomyelitis, and preparalytic poliomyelitis are identical?

If we turn next to the clinical picture of acute poliomyelitis it has been found useful in the past to illustrate this in the form of diagrams (figure 1). Such diagrams have in general been derived from series of childhood cases and yet they will do for purposes of introducing our subject here. Fever, vomiting and headache are common to both early and late phases of the disease and to the non-paralytic and abortive forms. Sore throat, it would seem, is a much more frequent complaint in the first phase than in the second [10] and thus becomes a useful symptom to orient the physician in determining with what stage of the disease he is faced. These early and sometimes transient signs of poliomyelitis, although designated in the past as *prodromata*, are actually critical indications that infection has started. From the very onset of fever the virus may already be in the central nervous system and the patient should be handled accordingly. More definite clinical signs of central nervous system involvement which may be heralded by paresthesias, vasomotor changes and pain in the limbs subsequently progress to the

* Definitions of the terms *abortive* and *non-paralytic* poliomyelitis are not easily made, particularly in this day and age when extensive muscle testing is carried out by specialists. Definitions used in our own clinic are: that an abortive case is a case of "minor illness" in which no clinical or laboratory signs of central nervous system involvement are detected. Obviously such a diagnosis can only be made during epidemics. The *non-paralytic* case is one in which such signs are present either in the form of stiff neck, or pleocytosis in the spinal fluid, etc., but that by the time three weeks from the onset of the illness has elapsed (the usual time of discharge from a hospital) no paralysis is detectable.

development of stiff neck and stiff back and transient hyperactive reflexes, etc. But these latter are *late* symptoms and signs as far as the progress of the infection is concerned and limited to the second phase of the disease.

In view of the changing aspects of poliomyelitis we find that the diagrams in figure 1, based as they are on the infantile forms of the disease, are inadequate. In particular they do not do full justice to the adult case. This has been borne out by Dr. Horstmann's recent studies made in the large epidemics occurring in this country in 1948 both in North Carolina and California. [11] She has demonstrated that the symptomatology of acute poliomyelitis differs in different age groups. For instance, the *diphasic course*,

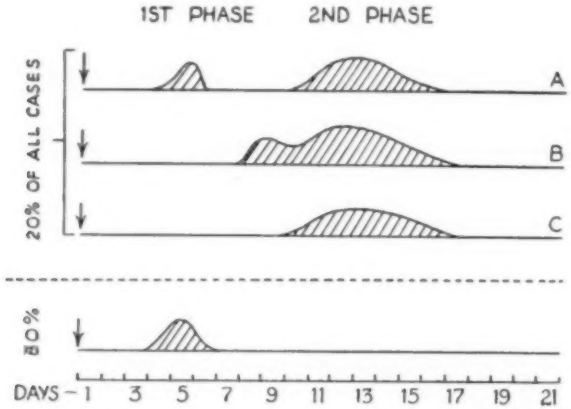

FIG. 1. Schematic diagram of various forms of the clinical picture which paralytic and other types of poliomyelitis may assume. Arrows on the left mark the hypothetical time of exposure to the virus. Forms, A, B and C illustrate both paralytic (and non-paralytic) poliomyelitis, with A as the dromedary type so common in childhood and C the "adult type" with a more insidious onset, and a picture usually limited to second phase symptoms. The lowest diagram is the usual type of abortive poliomyelitis with symptoms limited to those of the first phase. The 80 per cent ratio of abortive to 20 per cent paralytic (and non-paralytic) cases represent arbitrary figures. (From Horstmann and Paul. [10])

which has already been illustrated as classical, is essentially a manifestation of the disease in children under the age of 10 or 12. It is less common above the age of 14 (table 1). And again the *type of onset* seems to be different in young children from that of older children and adults. Pain in the back and an insidious onset are more apt to occur in patients who are over the age of 15 than under that age. Indeed below the age of 10 the onset of either or both phases is apt to be sudden in 80 per cent or more of the cases, whereas this is true in less than one-half of the cases who are above the age of 15. A gradual onset in an adolescent or young adult may be very puzzling to the clinician and even responsible for a considerable delay in diagnosis. Such cases were seen in the Army in World War II. The type of onset is illustrated in the following case report, which also appears in figure 2.

TABLE I

Shifts in the Clinical Picture in Relation to the Patients' Age
(after Horstmann [11])

Age	No. of Cases	Per Cent of Cases with:		
		Diphasic Course	Pain as an Early Symptom	Gradual Onset *
2–4	83	35	40	18
5–9	105	38	46	18
10–14	78	17	40	44
15–19	58	10	76	53
20+	59	12	76	66

* This refers, insofar as can be determined, to the onset of the *second* phase.

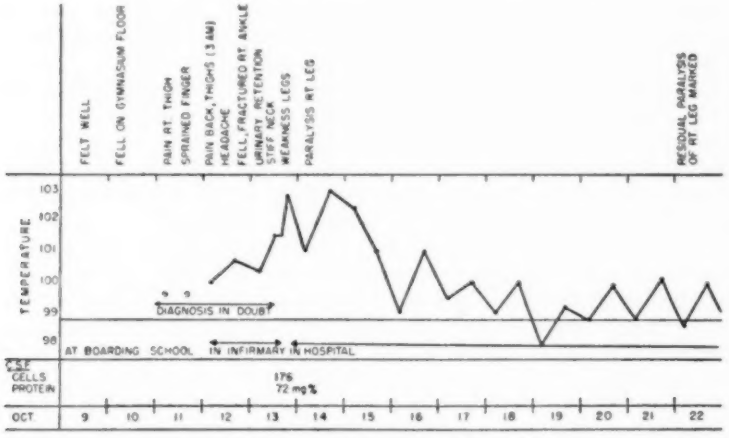

FIG. 2. Temperature chart of J. J., age 17, illustrative of the adult form of paralytic poliomyelitis with a gradual onset.

Case report of J. J., age 17, a pupil at a boarding school:

His illness occurred during a period when poliomyelitis was not epidemic in the local community. He was well on October 10 until he sustained a severe fall on the gymnasium floor. He was badly shaken and said he never felt "quite right" after that. On the following day he sprained his finger at football practice, but was able to continue playing football. On that night he awoke at 3:00 a.m. with a very severe pain, low down in his back, and made his way over to the school infirmary. His temperature was 100° at this time. Although numerous analgesics including opiates, were administered, this pain persisted all day during which he complained bitterly, and was very apprehensive. Fever was not appreciable at this time, remaining a little above 100°. The diagnosis was sprained back. On the following night, he got up out of bed in the dark to "relieve the pain," and fell. In the morning it was discovered that he had fractured his right fibula. During this period the low back pain continued. By mid-day of the next day (Oct. 13) his temperature had risen to 101°. Previously an orthopedist was called to look at the fracture. There seemed to be some stiffness

of the neck. At the same time, it was found that the patient could not void. The deep reflexes of both lower legs were increased at this time and there was a feeling of numbness in the left leg. He was removed by ambulance to the hospital some 25 miles away, still complaining bitterly of back pain, and by the time he was admitted his left leg was weak. The pain let up on the next day although fever continued and by this time severe paralysis of both legs had developed. At the time he was discharged from the hospital six weeks later, there was very little return of function to the legs. Paralysis of the bladder lasted for about four days, which was also the duration of his febrile period.

Such cases as that of J. J. have in the past been called the "straggling type" of poliomyelitis, a rather poor name but it illustrates the fact that the patient drags along for a few days with the diagnosis in doubt, and he may be subject during this prodromal period of his disease to a certain degree of exertion and trauma which according to Russell [12, 1] and others [13] exert a deleterious effect on the subsequent course of the disease. It is not clear just where the "straggling type" fits into the diagrams of the clinical picture of cases of poliomyelitis but it is compatible with form C in figure 1. It would seem that the first bout of fever, so common in the childhood case, is often absent in the adult case of this type, which begins rather insidiously by developing *second phase* symptoms such as stiffness of the limbs, paresthesias, transient sensory changes, and restlessness and pain, particularly pain in the back. These symptoms are responsible for many erroneous preliminary diagnoses, such as sprained back, renal colic, ruptured disc, etc.

Points in physical diagnosis of the second stage probably need not be repeated here. They center upon the appearance of pain or stiffness of the neck or back, pain in the limbs, and tightness of the hamstring muscles. The spine sign, the head drop, and observation of the abdominal, spinal and other reflexes are all important diagnostic tests. Early lumbar punctures may be helpful, but if there are no "central nervous system signs," the spinal fluid will usually be negative. A point of emphasis here is that, in spite of the fact that careful observation of these patients is strongly indicated at this stage of the disease, if one continually and repeatedly submits the patients to exhausting physical examinations and muscle tests, not to speak of multiple lumbar punctures, an element of exertion or trauma is introduced which is of no benefit to a patient who may be in a highly critical stage of his disease and who even may be hanging in the balance as to whether the virus will produce enough damage in the nervous system as to give rise to paralysis.

It is in this stage of *gradual* onset that the adolescent or adult patient may expose himself or herself to considerable strain on his own volition. It is not uncommon during the early days of poliomyelitis to see a patient who is restless and uneasy and feels driven to exercise or to go out and do things, in order to "shake off" a feeling of insecurity, stiffness or restlessness. The patient may even seek relief by walking the floor half the night or even attending a dance. Sometimes his pain at this stage is severe. Under such circumstances it is not relieved by mild analgesics. But in any event it is well to reiterate that, according to the estimates already mentioned, trauma

or exertion in these early days should be avoided and if the estimates are correct this protection of the patient becomes one of the most important therapeutic contributions that the doctor can make. In schools and camps, athletic directors should be aware of this fact, when poliomyelitis is about.

Management of Cases. One cannot be didactic about the treatment of poliomyelitis cases and particularly the treatment in the earliest stages. During epidemic times no clinician, however wise and experienced, can determine during the first few hours or days whether a given case in which the initial symptoms are limited to sore throat, headache, fever and vomiting will or will not go on to the eventual development of paralysis. But the clinician's responsibility with regard to the management of patients of any age who may be in the early stages of abortive or paralytic poliomyelitis seems clear. Thus all individuals with brief febrile illnesses during an epidemic of poliomyelitis should be regarded with suspicion, their physical activities should be curtailed and they should be treated more cautiously than usual and kept under observation for some 10 days. There is another reason why such cases deserve special consideration and why their activities might well be confined, which is, that regardless as to whether or not patients exhibit clinical signs of central nervous system lesions, there is a theoretical public health aspect to the non-paralytic case. For the degree of paralysis or the severity of central nervous involvement apparently bears no relationship as to whether or not the patient will excrete virus in his mouth or intestinal tract. It is not necessary for the attending physician to make a *public diagnosis* of poliomyelitis in order to observe a suspicious case for a week or 10 days. Indeed the physician may not even care to mention the possibility of poliomyelitis to the family, for families are prone to be apprehensive to the point of hysteria during an epidemic and anything which minimizes commotion is desirable. The local health officer may also object if the diagnosis is made too freely or made in the absence of orthodox diagnostic criteria. But this caution does not detract from the desirability of *observing* early and questionable cases most carefully for the development of "second phase" signs, and of regulating their physical activity.

The question as to whether *all* non-paralytic poliomyelitis cases should be hospitalized also raises interesting and controversial points. I am inclined not to recommend it for all patients although a tendency exists in some areas of this country at present to urge the hospitalization of all patients in whom a diagnosis of poliomyelitis (whether suspected or definite) has been made. And yet it is hardly necessary to point out that there are two views and in the event of an epidemic, one should not fill hospital beds with mild cases and thus exclude those who really need hospitalization. My own feeling is that the decision as to whether mild, non-paralytic patients may be best observed at home, will vary in different places and in different epidemics, depending upon the local facilities available for hospitalization and on the facilities for observing the patient at home. A special isolation hospital is not necessary for poliomyelitis patients. General hospitals can care for them

and should accept their community responsibility to do so. It is our belief that ordinary common sense isolation precautions should be carried out in connection with these patients but extreme precautions are not necessary. It has seldom been our experience to observe the spread of poliomyelitis within hospitals. The handling of the patients' stools in the same fashion as typhoid stools are handled is probably not indicated.

As for specific therapy,—there is none. Antiserum, chemotherapy, antibiotics—none of them seem to offer any help in the treatment of the acute poliomyelitis patient at present. The pain at the onset although it may be severe does not usually last very long. Strong analgesics are not very effective in the control of this type of pain and they would seem to be contraindicated. The application of moist heat remains as the most practical method of combating pain.[14] With its use, adequate fluid and salt intake should be kept up. I have had little direct personal experience with the use of prostigmin and of curare but would be inclined to regard them both as being still in an experimental stage. Any physician who has much to do with the clinical responsibilities in this disease knows full well of the pressure which is brought to bear by parents and well meaning friends, to do something definite, something positive or even new and spectacular in the way of treatment. My own feeling is that all meddlesome forms of therapy should be avoided because of their potential traumatic effect. Therapy which includes the use of strong purgatives seems contraindicated.

It will not be the function of this paper to consider the technical aspects of applying moist heat to combat pain and stiffness of the limbs and trunk. [14] That is a special chapter. Nor will it be my function to consider the changing concepts in the care and handling of paralyzed limbs or various other aspects of the paralytic form of poliomyelitis. Much of this aspect of therapy falls within the province of the orthopedist and belongs in the category of the after-care. [15] There are the special problems which occur with the bulbar form of the disease, in which the air passages must be kept as free from secretions as possible by postural drainage, suction, and, as a last resort, tracheotomy. [16] There are also special problems with respiratory paralysis which require the use of the respirator, and there are special problems with bladder paralysis. All require special types of handling.

A final point deserving emphasis is that during epidemics at least, it is expected that a *team* may be required for the proper handling of poliomyelitis patients. This team may be composed of an orthopedist, a physiotherapist, specially trained nurses, and others. In this team the physician must occupy his rightful place as captain during the early stages of the clinical course. He should not resign his captaincy until the case has definitely gone into the stage of after-care, and all the way through he should be on the alert to guard his patient from unnecessary trauma, exertion and above all from meddlesome therapy. The early therapy of poliomyelitis calls for an alert physician whose major responsibility is to guard his patient and to be ready for any serious emergencies.

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THE DIAGNOSIS AND MANAGEMENT OF ATYPICAL OR VIRUS PNEUMONIA *

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PRIMARY atypical pneumonia, or, as it is frequently termed, "virus pneumonia," has now become well-defined and established as a clinical syndrome. While it is probably not a new disease entity, it came into particular prominence in 1938 [1, 2, 3] following the introduction of sulfapyridine. This drug proved to be effective in the treatment of the true bacterial pneumonias, but not of other kinds of pneumonia, variously termed atypical bronchopneumonia, acute pneumonitis, atypical pneumonia, virus pneumonia, etc. The subsequent sulfonamide derivatives, and, more recently, penicillin, served further to differentiate the bacterial pneumonias from the syndrome now termed "primary atypical pneumonia," since these therapeutic agents were ineffective in the latter disease. Interest in and knowledge of this disease were heightened during the War to such an extent that approximately 300 papers dealing with the subject have appeared in the medical literature during the past 10 years.

It is therefore necessary only to summarize the generally accepted clinical picture of primary atypical pneumonia,[4, 5, 6, 7] before considering certain aspects of the diagnosis and management of these cases.

Primary atypical pneumonia may be described as an acute respiratory infection that begins gradually and insidiously with complaints of symptoms referable to the upper and lower respiratory passages, or of constitutional symptoms such as headache, feverishness, chilliness and malaise. Cough is generally prominent and the sputum is mucopurulent, without blood. On physical examination, the indication of pneumonia is characteristically the presence of medium moist râles in the absence of signs of true consolidation. Radiographically, the pulmonary infiltration is variable in extent, but is often greater than either the patient's appearance or the physical signs in his chest would suggest. The total leukocyte count and differential ratio are usually within normal limits. Pathogenic bacteria commonly causing pneumonia are absent. The course is variable, yet benign; the fever is moderate and of either sustained or remittent character, and the pulse and respiratory rates are relatively low. The duration of illness is usually not more than two or three weeks and recovery is complete, without complications. In approximately one-half of the cases cold hemagglutinins and agglutinins for streptococcus MG appear in the sera during convalescence.

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Epidemiologically the cases tend to occur sporadically, and case-to-case spread is seldom apparent. There is generally a seasonal rise in incidence during the winter months in association with an increase in the total respiratory disease rate. Some evidence indicates that the incidence varies from year to year in different geographic areas.[5, 9] The behavior of the disease suggests that the causative agent may induce pneumonia in only a small proportion of the infected individuals, the larger proportion suffering merely from a mild respiratory illness. No reliable figures giving the true incidence of primary atypical pneumonia in large civilian populations are available, but the attack rate in military forces during the past War averaged approximately 10 per 1,000 per annum, exceeding by almost 10 times the incidence of pneumococcal or bacterial pneumonia.

This brief description obviously presents the average or median characteristics of primary atypical pneumonia and neglects the extremes. One of the interesting and at times puzzling features of the disease is the variability of the infection, not only in severity, but also in the clinical features presented by many patients. It may simulate bacterial pneumonia, Q fever, and a variety of other pulmonary infections, as well as neoplastic diseases of the lung, pulmonary edema, and other non-infectious processes. It may take the form of a prolonged, low-grade infection or of a short, acute illness terminating almost abruptly. In other instances, neither a diagnosis of primary atypical pneumonia nor of other known disease processes can be established. The following cases illustrate some of the variations and the resulting diagnostic problems.

The first patient presents a problem in the differential diagnosis of pneumococcal pneumonia and primary atypical pneumonia (figure 1). He was a 43 year old white male who was admitted on the third day of an acute illness initiated abruptly by a shaking chill, and characterized by fever, pleural pain in the right chest posteriorly, and mucopurulent, slightly blood-tinged sputum. He had had a mild cough for one month and had suffered from asthma for 10 years.

On admission the patient did not appear to be seriously ill. His respiratory rate was 20. There were signs of true pneumonic consolidation over the area of the upper portion of the right lower lobe. The total leukocyte count was 12,300, 86 per cent of which were neutrophiles. The type III pneumococcus was isolated from the sputum by mouse inoculation, although it could not be found on direct examination (Quellung). Sulfadiazine was administered because of presumed sensitivity of the patient to penicillin. On the ninth day of illness pleural pain appeared in the right chest anteriorly in association with extension of the infiltration to the right middle lobe. The leukocyte count rose to 22,600, of which 90 per cent were neutrophiles. Penicillin therapy was instituted. The temperature gradually declined to normal. Serological studies revealed a cold hemagglutinin titer of 256 on the third day of illness, a titer of 512 on the tenth day, and a subsequent fall to levels of 32 and 64. Agglutinins for streptococcus MG failed to develop.

Sera obtained on the tenth and eighteenth days of illness protected mice against 100 minimal lethal doses of pneumococci, type III.

The diagnosis of this illness cannot definitely be established. The physical signs were those of pneumococcal pneumonia, yet the patient's general appearance and his course were more characteristic of primary atypical pneumonia. The laboratory findings likewise are not conclusive. The presence of small numbers of type III pneumococci in the sputum does not establish this illness as pneumococcal pneumonia, particularly since the type III pneumococcus is one of the common carrier types. The patient may have suffered from primary atypical pneumonia, from pneumococcal pneumonia, or, possibly, from both diseases.

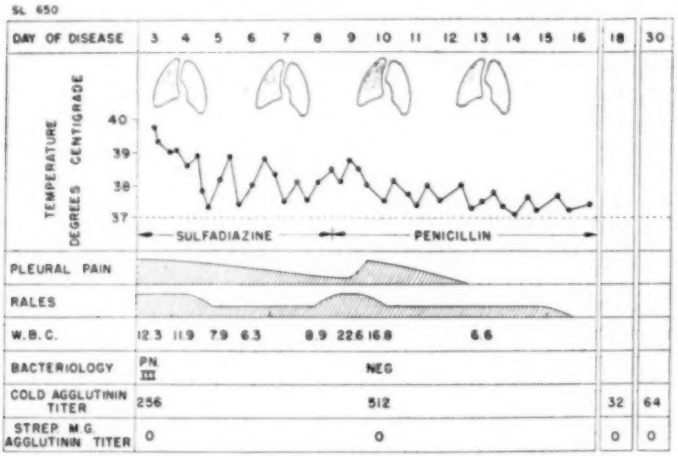

FIG. 1. Clinical chart of a patient whose illness illustrates the problem of differential diagnosis of primary atypical pneumonia and pneumococcal pneumonia.

The next two patients illustrate both the diagnostic problem and the prolonged, low-grade nature of "atypical pneumonia" in the older age group. One of the patients (figure 2) was a 70 year old white female who became ill rather suddenly two weeks before admission. The first symptom was a moderately severe cough productive of gray, mucopurulent sputum. Weakness, fatigue, low-grade fever and gradually progressive anorexia ensued. Penicillin was ineffective. On admission, physical examination revealed medium fine râles at both bases posteriorly and roentgenogram showed infiltration of the left lower lobe. The course was characterized by a slow and gradual improvement not influenced by therapy with aureomycin.* No pathogenic bacteria were isolated. Neither cold hemagglutinins nor ag-

* Furnished by the Lederle Laboratories Division of the American Cyanamid Company.

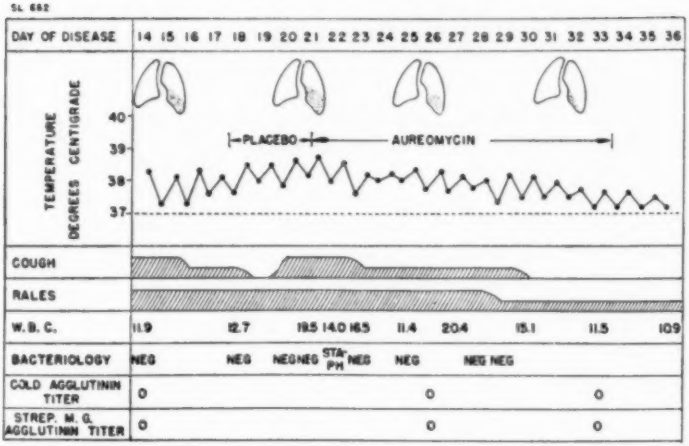

FIG. 2. A prolonged, low-grade type of primary atypical pneumonia in an elderly patient whose illness was not influenced by therapy with aureomycin.

glutinins for streptococcus MG developed. No underlying organic disease was detected.

The other patient (figure 3) was a 69 year old female whose illness began with a productive cough three weeks before admission and was characterized by fatigue, mild malaise and low-grade fever. On the day before admission she had a severe bout of coughing and wheezing attended by marked respiratory distress. Penicillin was administered on the day of admission.

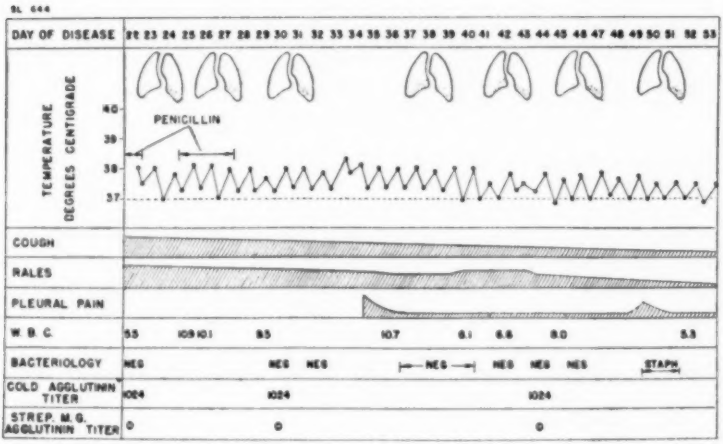

FIG. 3. A prolonged, low-grade type of primary atypical pneumonia in a 69 year old woman.

Physical examination on admission revealed coarse and sibilant râles throughout the chest and medium fine râles in both lower lobes. Fine râles were later heard over the left upper and right middle lobes, associated with apparent spread by roentgenogram. Pleural pain and a friction rub appeared over the right middle lobe on the thirty-sixth day, and gradually subsided with an exacerbation on the fiftieth day. Penicillin was without effect. A cold hemagglutinin titer of 1,024 persisted throughout the hospital stay.

Presumably both of these patients illustrate a prolonged and low-grade form of primary atypical pneumonia. In one instance cold hemagglutinins were absent, in the other a high titer had developed by the end of the third week of illness. Neither patient harbored the pathogenic respiratory bacteria commonly associated with bacterial pneumonia.

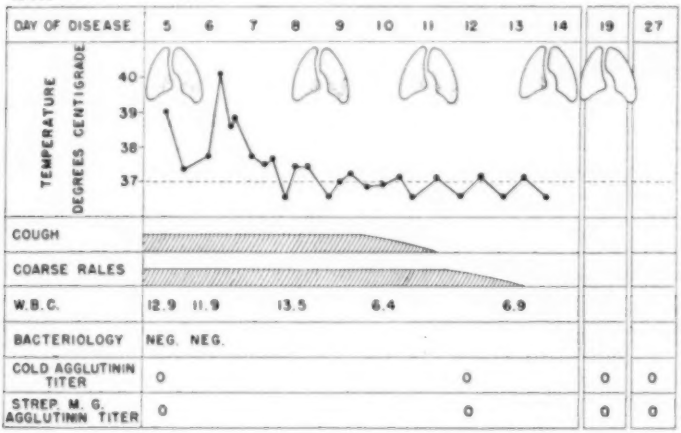

FIG. 4. Moderately severe primary atypical pneumonia in a young adult man whose fever subsided within a period of 48 hours without therapy.

The remaining two cases (figures 4 and 5) are presented to illustrate the opposite extreme in variation. In both of these patients the illness was moderately severe and of approximately a week's duration. In both defervescence occurred sharply over a period of 48 hours and the temperature remained at a normal level during convalescence. In other respects, however, the illnesses conformed to the general picture of primary atypical pneumonia.

Differential diagnosis of primary atypical pneumonia therefore requires an appreciation of the great variability in the infectious process as well as of the variety of causes of this clinical syndrome. There is as yet available no specific laboratory test, based on the causative agent, to give direct confirmation of the diagnosis of primary atypical pneumonia. Nor is there

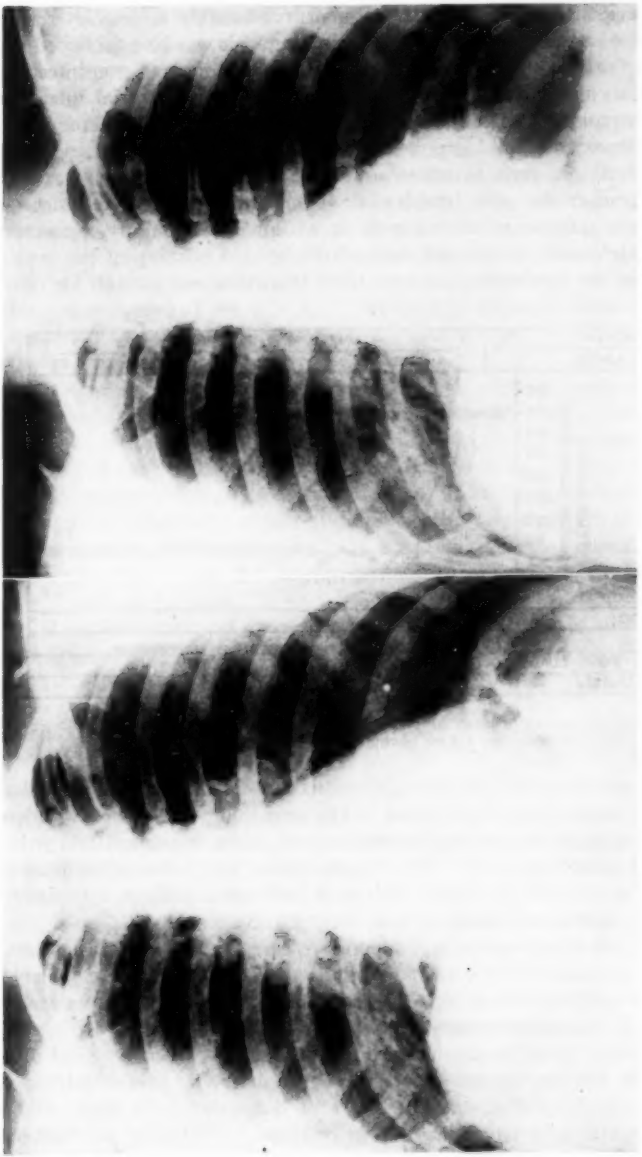

FIG. 5. Moderately severe primary atypical pneumonia in a young adult male whose febrile illness terminated rather abruptly during a period of 48 hours.

conclusive evidence that only a single agent, presumably a virus, is responsible for these cases. A reasonably certain diagnosis can be established only by excluding other causes for the illness, both infectious and non-infectious. The list of such infectious agents is long and includes bacterial infections, such as tuberculosis, tularemia and the bacterial pneumonias; fungous infections, such as coccidioidomycosis; rickettsial infections, such as Q fever; parasitic infections, such as schistosomiasis; and virus infections, such as influenza, psittacosis, and lymphocytic choriomeningitis. Non-infectious causes include pulmonary edema with or without heart failure, pulmonary infarction, atelectasis, neoplasms, sarcoidosis, etc. Considering the over-all occurrence of the syndrome, however, these known causes account for only a

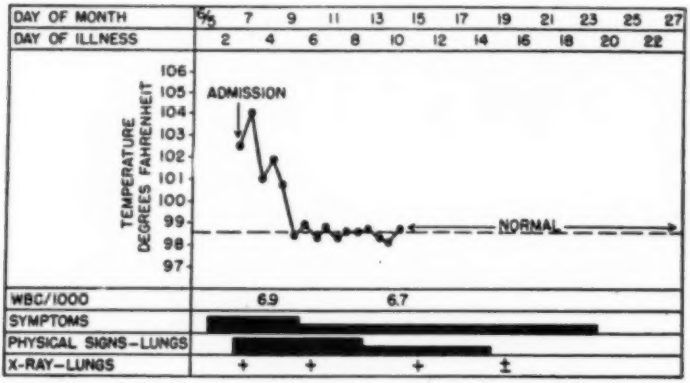

FIG. 6. Moderately severe primary atypical pneumonia in a young adult male whose febrile illness terminated rather abruptly during a period of 48 hours.

relatively small proportion of the total number of cases and a definitive diagnosis can be reached in most of them. The remaining cases, now considered as primary atypical pneumonia, are numerically most important and will be encountered most frequently. It is highly important, however, to keep the differential possibilities in mind with each individual patient, especially in view of the rapid development of new therapeutic agents.

The general symptomatic and supportive care for patients with primary atypical pneumonia is well known. Only two aspects of the management of this disease will therefore be considered here, namely, the questions of isolation and of specific therapy.

Epidemics of primary atypical pneumonia and case-to-case spread of the infection are infrequent, but they have been observed, particularly in institutions, schools, and among the staffs of hospitals.[3-7] A few instances of multiple cases in a family have been reported.[3, 7] During the winter of 1947 to 1948 in Cleveland, Jordan [10] observed 19 families in which multiple cases of atypical pneumonia and associated respiratory infections occurred, apparently as the result of household spread. Of the 83 persons in these

families, 60, or 73 per cent, had a respiratory infection and 29 of these were established as primary atypical pneumonia. Because of such examples of apparent contact spread, the question is frequently raised as to the need for isolation. From the evidence now available, however, there is little reason to believe that isolation would be effective in most circumstances, with the possible exception of a hospital in which epidemic spread is occurring. The great majority of cases still occur in a sporadic manner. The incubation period is long, approximately two to three weeks, and the period of infectiousness has not been defined. Moreover, the frequent occurrence of mild, non-pneumonic forms of illness probably due to the same agent indicates that isolation of only those patients with pneumonia would have little effect on the spread of the infection. At the present time, therefore, it seems reasonable to continue to handle these cases without strict isolation precautions.

The question of specific therapy in primary atypical pneumonia is now in the process of reëvaluation. The efficacy of any therapeutic agent has been and continues to be extremely difficult to determine, because of the variability of the clinical course and the difficulty of establishing a firm diagnosis by the laborious methods of exclusion. For these reasons the failure of an agent to alter the course of illness and to prevent spread of infiltration in a few patients is probably more indicative of the true worth of the agent than is apparent success in a larger number of cases, as Finland, Collins and Wells [11] have emphasized.

Convalescent sera and gamma-globulin have been used to a limited extent for therapy of primary atypical pneumonia.[7, 9, 12–15] These agents have not been evaluated adequately, but it seems probable that they are not very effective.

Sulfonamides, and likewise penicillin, have generally been found to have no effect on the course of the infection. In cases where the diagnosis is in doubt, however, it is advisable to administer penicillin after the diagnostic procedures have been carried out. The lack of a definite response within 72 hours is usually an indication to discontinue the drug unless a bacterial etiology has been established. The administration of sulfonamides or penicillin is frequently suggested for the prevention of secondary bacterial infections. If the diagnosis of primary atypical pneumonia is reasonably certain, the value of such therapy is very questionable. Secondary bacterial infection is an extremely rare complication, occurring less frequently than toxic reactions to the drugs. Its occurrence, moreover, is usually obvious clinically and can be readily confirmed before or coincidental with the administration of specific therapy at that time.

There are few reports of the use of streptomycin in the treatment of primary atypical pneumonia, although this antibiotic agent is generally thought to have no effect on the course of the disease. Finland, Collins and Wells [11] have reported two cases in which defervescence and clinical improvement followed promptly upon administration of streptomycin. Further data are needed to permit evaluation of this agent.

Recently, three groups of investigators have reported the treatment of primary atypical pneumonia with aureomycin.[11, 17, 18] The three series were not controlled, but comprise 43 cases reported in detail, of which 42 showed clinical improvement within three days after administration of the drug. The diagnosis was supported in the majority of the cases by the development of cold hemagglutinins. These results are highly encouraging, despite the difficulties of evaluating therapy in any individual patient. In view of the great variability of the disease, however, it is essential that further critical trials, and, if possible, controlled studies, be carried out before aureomycin is accepted as a specific remedy for primary atypical pneumonia.

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SYNCOPE: A REVIEW *

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Introduction

This discussion of syncope is divided into three parts: first, a brief consideration of the subject, second, a description of the various syndromes, and third, a review of some biological aspects of the reaction in certain instances. The work of Weiss and his associates [1] forms the basis of our present knowledge; his classical review in the Oxford Medicine was written about 1937. Since then the chief contributions have come from Engel and Romano [2, 6] who have not only utilized the relatively new technic of the electroencephalogram, but have also studied fainting from a modern psychological point of view.

Fainting is so common that we tend to disregard it; so it is well to point out at the onset that transient benign syncope and fatal syncope are probably based on the same mechanisms. Instantaneous death is not uncommon, but at autopsy we rarely find anything to explain it. Evidence of chronic structural abnormalities is often found, particularly in the heart, but such abnormalities are not incompatible with life and are found frequently when they did not contribute to the cause of death. Thus the evidence points towards the concept that instantaneous death is often fatal syncope, ventricular fibrillation or asystole of various types. Moritz [2] has made the interesting suggestion that the so-called thymo-lymphatic deaths are probably instances of fatal syncope due to hypersensitivity of certain reflexes.

In normals the sensitivity of reflexes may vary strikingly, and in disease it may be markedly increased. This applies to both physical and functional diseases. Likewise, in disease the compensatory recovery mechanisms following reflex changes may be slow or may fail altogether. Such increased sensitivity may occur at either end of the reflex arc and possibly at the site of the central connections. Little is known about the reactions at the sensory end of the arc, but at the motor end a few of the changes involved in translating the neuro-chemical impulse into muscular or glandular response are now understood to some degree. The acetylcholine-choline esterase system is perhaps the best known example.

Syncope collapse and shock should be considered as a continuum rather than as separate entities. The common denominator is best described as a discrepancy between the volume of the circulating blood and the capacity of the vascular bed. This concept holds for all the cardiovascular types of syncope. A review of the factors producing such a discrepancy suggests a

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rough separation into those involving primarily the pumping apparatus and those involving the pipe line system. Pumps fail from troubles in rate, in valves, and in output of power. A group of pipe lines contained in a housing of some sort may leak to the outside or may leak into the spaces between the pipes, or the number and size of functioning pipes may be increased or decreased. Thus capillaries may shut down entirely, or they may dilate to some two and one-half times their usual normal size. This last possibility reminds us that biological plumbing, like modern plumbing, is complicated by intricate electrical control devices, and in the majority of syncopes due to pump or pipe line troubles we find the nervous system involved. And further we discover that in some instances the pump and pipe lines are not involved at all, the trouble being solely in the electrical system. This then forms the basis of a tentative classification. Its value is slight; it serves merely to orient us in the attempt to make order out of chaos.

1. Electrical:
    1. Hypoglycemia.
    2. Epilepsy.
    3. Hysteria.
2. Pump:
    - Rate:
        1. Tachycardia.
        2. Adams-Stokes syndrome.
        3. Reflex—vagus to vagus (so-called vago-vagal type).
        4. Reflex—carotid sinus to vagus.
    - Valves:
        5. Valvular damage.
    - Motor:
        6. Myocardial weakness.
3. Pipe Lines:
    1. Reflex—psyche to peripheral vascular bed (vaso-vagal or vaso-depressor type).
    2. Reflex—carotid sinus to peripheral vascular bed, and to cerebral vascular bed.
    3. Postural hypotension (normal reflex failure).
    4. Collapse and shock.
    5. Miscellaneous rarities.

Description of Syndromes

It is not the intention that this review should be a German "Handbuch" with detailed pictures of the various syndromes. These are available in the literature. Exceptions will exist to many of the general statements which follow because of the frequency of complicating factors in many types of syncope. Such omissions are justified because an overall picture of syncope is our immediate purpose.

A. Syncope due to electrical trouble without involvement of the pump or pipe lines.

1. *Hypoglycemia.* This is included as a sop to tradition. The respiratory quotient of brain tissue is 1, suggesting that only sugar is metabolized. Oxygen consumption of the brain has been shown to be markedly reduced during unconsciousness due to hypoglycemia. We assume, therefore, that the decrease in oxidation of carbohydrates does not allow sufficient chemical activity to support consciousness.

2. *Epilepsy.* Faints and fits are notoriously hard to tell apart. It is generally stated that faints have cardiovascular involvement, no aura, occur in the upright position, have no associated convulsions, are followed by prompt recovery and are not apt to recur. And it is generally stated that fits have a neurogenic etiology without cardiovascular signs, have an aura, occur in any position, have associated motor phenomena, are followed by subsequent confusions and are apt to recur. These statements hold true in the majority of instances but there are exceptions. Faints may be accompanied by such phenomena as auras, convulsions, micturition, defecation, injuries, and subsequent confusion. They may recur, and they may occur in the horizontal position. Likewise fits may be accompanied by little or no convulsive movements, there may be marked vasomotor changes, and emotions may precipitate them. Thus the differential characteristics are relative and not absolute. Electroencephalograms are a great help in sorting out these borderline states.

3. *Hysteria.* We are indebted to Engel and Romano [5] for their recent delineation of this syndrome. Practically all types of fainting we will consider, except this one, involve the cardiovascular system, are due to cerebral anoxia, and show electroencephalographic changes. Here, however, the usual muscular and vascular symptoms preceding the common faint are absent. The subject loses consciousness in an abrupt and dramatic manner with no cardiovascular changes, no respiratory changes, and no electroencephalographic changes. This type of fainting occurs more frequently in women, and is often but one of several hysterical manifestations. It usually occurs when the subject is in the presence of others, no injuries are sustained from a fall, and unconsciousness may persist for as long as an hour or so despite a prone position. Its actual incidence is not known but it is probably much less common than the usual vascular type of fainting.

For those who struggle with psychosomatic terminology this is an important syndrome because it is purely psychological; it is an hysterical symptom in pure culture. On the other hand the usual faint has associated cardiovascular changes and is an organ neurosis. The basic cause of the usual faint is equally psychological but the mechanism of production of the symptom is different, involving the autonomic nervous system and measurable physiological changes. These two types of fainting, pure conversion hysteria and pure organ neurosis, have been considered as representing the two ends of a spectrum, whereas many of our psychosomatic illnesses fall

somewhere in between and represent mixtures of varying degree of hysteria and organ neurosis. Few clinical syndromes allow of such clear delineation and objective proof as these two types of fainting.

B. Syncope due to pump troubles. These cardiac disturbances may be due to disease processes within the heart, or to reflexes reaching the heart via the vagus, or to a combination of both factors.

1. *Tachycardias.* There is little to say about this group. It is well known that under these circumstances the pumping action of the heart is highly inefficient. Of a hundred reported cases, 15 had cerebral symptoms. This included four cases of syncope, two of which had convulsions.

2. *Adams-Stokes syndrome.* This term is used in its commonly accepted meaning of damaged conduction system with partial or complete heart block. If the block is partial the attack of syncope is usually due to the sudden onset of complete block with delay in formation of the idioventricular pacemaker. If the block is complete the attack may be due to one of several changes, a temporary inhibition of the ventricle pacemaker, a sudden shift in the location of this pacemaker with a further reduction of an already slow rate, or transient runs of premature ventricular contractions. The degree of existing cerebral sclerosis is important here as evidenced by the fact that anywhere from 3 to 15 seconds of asystole may be required to produce syncope. It is the function of the total cardiovascular apparatus in oxygen transport that counts, and not the heart rate. A rate of 30 is perfectly compatible with health, but a sudden change to a rate of 30 may produce syncope because compensatory reactions occur too slowly to maintain an adequate cerebral circulation. As is well known, ephedrin increases ventricular irritability and markedly reduces the frequency of attacks.

3. *Reflex*—vagus to vagus (so-called vago-vagal type). This is a most important group because it contains the fatal and often preventable syncopes. The afferent limb of the reflex arc may be anywhere in the wide area served by the sensory component of the vagus. The efferent limb consists of the motor fibers in the vagus which run to the heart. The result of impulses transversing this arc is a sudden change in cardiac rate. This type of syncope due primarily to vagal cardiac inhibition has been called Adams-Stokes syndrome of reflex origin. It is true that this title is historically justified, because both Adams and Stokes described cases in which the heart rate suddenly slowed to the extent that the patient fainted. The actual mechanisms in their cases will never be known. However, our thinking will be clearer if we follow common usage and the dictionary, and restrict this somewhat obnoxious title to syncope associated with organic heart block. The specific effect of vagal inhibition on the heart varies tremendously. Some order can be made of it if we consider the three possible sites of impulse formation, the SA node, the AV node and the ventricular conduction system. In any of these areas impulse formation or impulse transmission may be slowed or stopped altogether, and in two of them fibrillation may possibly be initiated. Thus we have SA slowing, SA block and possibly auricular fibrillation, AV

slowing, AV block, and ventricle slowing, ventricle block and ventricle fibrillation.

A well known example of this reflex arc is so-called pleural shock. A controversy formerly existed as to whether this syndrome was due to reflex changes or to air embolism. The latter theory was discarded because of the following points: (1) experimental work favors the reflex theory, (2) the unilateral neurological signs sometimes seen in pleural shock, and called on to support the air embolus theory, are also seen in the cerebral type of carotid sinus syndrome, (3) a very nice bit of clinical investigation has demonstrated that during the performance of initial pneumothoraces a fall in blood pressure and pulse rate occurs only as the needle encounters the unanesthetized parietal pleura. Anesthesia of the pleura or a prior injection of atropine abolishes this vascular response. Pleural shock has occurred under many circumstances such as chest taps, irrigation of cavities, moving of drains, and blows on the chest wall. Mechanical irritation such as needling has been shown to give a more intense reflex if the pleura is inflamed.

The afferent limb of this reflex arc may arise in the esophagus. Weiss[1] records the case of a man who for 10 years had suffered from frequent fainting on swallowing, and finally was hospitalized after a suicidal attempt. A diverticulum of the esophagus was found, and the syncopal attack, which was due to transient AV block, could be reproduced by the distention of a balloon in the esophagus. Ephedrin abolished the unduly slow rate, atropine abolished the AV block, and eventually a surgeon abolished the diverticulum.

Similar reflexes may arise in the walls of the bronchi, and sudden changes in cardiac rate have been reported during bronchoscopy and at operation. Stimulation of the auricular branch of the vagus is known to produce cough but also may produce syncope. Various procedures during abdominal operations may produce slowing of the heart rate and transient asystole. Such reflexes may arise in the heart itself, and this constitutes one of the problems of cardiology. Many patients with infarctions who survive the initial shock die very suddenly in hours or days, probably with ventricular fibrillation. Quinidine has been advised to diminish ventricular irritability, thus rendering the end organ less susceptible to vagal stimulation, and atropine has been advised to block the reflex arc at the nerve ending. In experimental myocardial infarctions atropine apparently does reduce mortality but data in humans are difficult to obtain.

4. *Reflex*—carotid sinus to vagus. There is no essential difference between this and the vagus to vagus reflexes just discussed. It will be considered later with the two other types of carotid sinus syncope.

5. *Valvular damage.* Advanced valvular heart disease with obstruction, such as mitral and aortic stenosis, and congenital narrowing of the aorta may be associated with syncope on exertion. It would seem that an inadequate cardiac output was at fault but there is evidence to show that reflex factors are present in addition. Cases of aortic stenosis characteristically

die suddenly without demonstrable cause, and this type of death supports the contention that reflex factors play an important rôle.

6. *Myocardial weakness.* Cases of paroxysmal nocturnal dyspnea and acute pulmonary edema due to left ventricle failure may suddenly lose consciousness. Again it is probable that reflex and mechanical factors combine to produce the syncope.

Unfortunately the situation at times is more complicated than this description of a single reflex arc suggests. In the first place our knowledge of the sensory components of the vagus is very scanty and the afferent limb of the arc may sometimes lie in the sympathetic system. In the second place it has been demonstrated that the efferent limb is not solely vagal with resultant cardiac inhibition but may also be sympathetic with peripheral vasodilatation. For practical purposes, however, the chief effect is the vagal one. Therapeutically, it is very important that these patients receive atropine, particularly if they are elderly or nervous, or both. If tolerated 1 mg. (1/75 gr.) is preferable to the usual 0.5 mg. (1/150 gr.).

C. Syncope due to pipe line trouble.

1. *Reflex*—psyche to peripheral vascular bed (vaso-vagal or vasodepressor type). This is the common fainting that is so familiar to all of us, that occurs after prolonged standing or with a venipuncture. The classical swoon of the Victorian lady probably belongs in this category. The fainting results from cerebral anoxia which follows an increase in the capacity of the vascular bed with resultant inadequate venous return and inadequate cardiac output.

The factors affecting this mechanism are numerous and can be divided into physical and psychological. In brief the physical factors include such things as infections, heat, debilitation, malnutrition and anemia, vomiting, first trimester of pregnancy, mountain sickness, instrumentation, inadequate circulation from any cause, paracentesis with resultant pressure changes, chemical factors such as spinal anesthesia or nitrites, and prolonged maintenance of the upright position. The psychological factors consist of the witnessing of accidents, injuries or mutilation, the learning of tragic news, the experiencing of minor surgical procedures including venipuncture, suggestion and possibly pain. Pain alone is not an adequate stimulus; we shall see later that pain actually reverses the mechanism.

Fainting can be experimentally produced in susceptible patients by means of a tilt table, or in any subject by means of a tilt table plus emotional stimuli or vasodilating drugs such as sodium nitrite. The associated symptoms and signs are easily studied under such circumstances. They consist of peculiar epigastric sensations, weakness which soon becomes extreme, light headedness or giddiness, yawning, sighing respiration, pallor, sweating, sometimes headache or tinnitus, precordial discomfort, and hyperperistalsis with attendant cramps, nausea or belching. Sometimes just before the onset of syncope there is a sense of coldness or numbness starting at the periphery and moving centrally. Then the sudden loss of consciousness

occurs followed by convulsions if the subject is not tilted back to the prone position. Nothing so resembles death; the pallor is ghastly and the pulse weak to absent. Just before the onset of syncope the subject may experience anxiety and a fear of impending dissolution, symptoms which remind us of myocardial infarction. Indeed the mechanism of production of such sensations by the autonomic nervous system is probably the same in both instances. Physiologically, the symptoms occur during a period of falling systolic pressure and diminishing cardiac output. The diastolic pressure is maintained, or even rises, which means that the essential change is a diminution in pulse pressure. Meanwhile the pulse rate increases and then just prior to syncope there is the precipitous fall in both blood pressure and pulse rate. The classical bradycardia is a secondary phenomenon because the slowing of the pulse can be prevented by atropine without interfering with the production of the faint. Gravity determines only the final drop in blood pressure as all the other changes may be seen in the prone position. It is important to remember that the reaction may continue long after the stimulus is withdrawn, even for two to three hours.

In the brain no changes are observed by electroencephalogram until unconsciousness occurs; then the normal fine waves are replaced by large slow waves which persist until consciousness is regained.

Despite our habit of discoursing in a learned manner about peripheral vasodilatation the nature of the changes which occur in the peripheral vascular system is not known. All we do know is that the blood ceases to return from this hinterland. It has been demonstrated recently that as much as 1.5 liters of blood may be held in the muscles during syncope. Whether there is active vasodilation in the muscles under such circumstances, or simply passive vasodilation due to vasoconstriction elsewhere, is not known. Finally, the highly important factor of the effect of muscle tonus on the capacity of the venous bed has not been quantitated.

Recovery mechanisms consist of the abolition of the effect of gravity by the fall, by convulsive movements which have a muscle pumping effect on venous blood, and possibly certain other reflexes which arise centrally as a result of cerebral anoxia. Sudden death may conceivably result from the failure of these recovery mechanisms. Engel [3] has demonstrated that following a faint the signs and symptoms are prolonged by lying motionless, but may be reversed by exercising in the prone position. The importance of exercise is also demonstrated by the ease with which syncope may be produced in an athlete by having him stand motionless immediately after violent exercise. Fainting is common during various painful procedures, but in the experimental subject it can be demonstrated that pain tends to reverse the reaction. The time honored remedies of a bucket of cold water, slapping the face, ammonia, and even the Victorian chafing of the wrists have the sound theoretical basis of stimulating sympathetic and muscular activity.

2. *Reflex*—carotid sinus to peripheral vascular bed, and to cerebral vascular bed. Just beyond the bifurcation of the common carotid the internal

carotid artery shows a slight bulging. Here in the arterial wall are specialized end plates affected by pressure changes, and a rich nerve plexus with central connections via the glossopharyngeal nerve. Very close by lies another structure, the carotid body, which is affected by chemical changes in the blood. Two comparable sensory receptors lie in the arch of the aorta. Thus there are the carotid and aortic nerves responding to pressure changes and the carotid and aortic bodies responding to chemical changes. This is the grossest of generalizations but is adequate for our purpose. These end organs constitute important buffers of the cardiovascular system, emergency regulators with a restraining influence preventing undue change, particularly undue elevation of blood pressure and pulse under conditions of physiological stress.

Mechanical stimulation of an unduly sensitive carotid sinus nerve plexus causes syncope by three very different mechanisms. The afferent limb of the reflex arc is the same in each of these three, consisting of the nerve plexus in the wall of the carotid sinus and the glossopharyngeal nerve.

In the first group the efferent limb consists of sympathetic nerves to the peripheral vascular bed with the vasodilatory or so-called vasodepressor effect, the mechanism of which has just been discussed. Ephedrin will decrease this response to some degree.

In the second group the efferent limb is made up of cardio-inhibitory vagal fibers. It belongs, therefore, under the heading of pump troubles. This carotid sinus to vagus reflex occurs chiefly in the elderly arteriosclerotic group. It has been definitely demonstrated that digitalis increases the sensitivity of the reflex, and one should remember this in digitalizing elderly patients. Increasing the irritability of the heart with ephedrin helps to prevent attacks, but blocking the vagus terminals with atropine is much more effective.

In the third or so-called cerebral group the efferent limb of the reflex arc lies in the brain itself and its course is unknown. The attacks occur without changes in blood pressure or in cardiac rate, and atropine and ephedrin are without effect. Induced attacks occur three or four seconds after mechanical stimulation of the sinus, whereas in the other two groups, the lag is from 12 to 16 seconds. No changes can be demonstrated in total cerebral blood flow, but there is now evidence pointing to localized vascular changes in the brain. The same electroencephalographic changes occur as with vasodepressor syncope, but usually they occur only on the contralateral side, although they sometimes may be bilateral and rarely homolateral. This unilateral affect you will remember has also been noted in pleural shock but there its mechanism has not been worked out. This type of carotid sinus syndrome occurs in younger patients who usually show the stigmata of vasomotor instability, such as palmar sweating, palpitation, fluctuating blood pressure, dermatographia, and so forth.

Only some of the factors which produce increased sensitivity of the carotid sinus reflex are known. Instability of the autonomic nervous system

is apparently a factor in the cerebral group. Occasionally organic lesions are present, tumors or aneurysmal dilatation of the carotid artery. Arteriosclerosis seems to increase sensitivity, and digitalis may do so. In days gone by high stiff collars were at times a sartorial hazard. If drug therapy is inadequate in the vasodepressor and vagal types, surgical ablation of the nerve plexus is usually effective.

3. *Postural hypotension* (normal reflex failure). This is commonly seen as a mild fleeting affair in cases of vasomotor instability, and is now encountered following sympathectomy for hypertension. It occurs rarely with spinal cord diseases, such as tabes, which may involve the sympathetic pathways. Normally, when a subject suddenly assumes the erect position both systolic and diastolic pressures rise and the pulse rate rises. Here both mechanisms fail. The pressures actually fall and the pulse rate fails to rise. So far as is known poor vasomotor tone with sudden pooling of venous blood is responsible. Rubber bandaging of the lower extremities is the most effective therapeutic procedure.

The effects of centrifugal force are comparable to those of gravity, and have been extensively studied by aviation physiologists. The well known G is defined as a force equal to that of gravity. The sensations of a person subjected to increasing centrifugal force are as follows:—at 2 Gs the hands and feet feel heavy and there is increased pressure of the buttocks against the seat; at 3 to 4 Gs there is an exaggeration of these symptoms and the head is held up with difficulty; at 5 Gs the subject can hardly move and has trouble breathing, and between 7 and 8 Gs there is the sudden "blackout." Pulse and blood pressure responses have been studied under these circumstances, and a constant lag has been demonstrated of from 10 to 15 seconds between the application or removal of the force and the cardiovascular response. This is comparable to the 12 to 16 seconds lag in the vasodepressor type of carotid sinus syncope, and shows the characteristic time period for the induction of the diminished venous return—diminished cardiac output cycle. The hydrostatic effect at 5 to 8 Gs is such that the usual compensatory mechanisms are helpless. Armstrong [4] reproduces some remarkable serial chest roentgen-rays of a monkey before and during the application of a centrifugal force of 5 Gs. As the force is applied the heart shadow almost disappears, suggesting that venous inflow has almost ceased. Abdominal supports increase the subject's tolerance by ½ to 1 G, and pressurized suits have a somewhat greater effect. With the increasing air speeds now becoming available this problem is of great importance to the fighter pilot, because it represents the chief factor limiting maneuverability.

4. *Collapse*. This constitutes an ill defined intermediate stage between syncope and shock. Here as in the vasodepressor type of syncope we are concerned primarily with an increased capacity of the vascular bed, rather than with disturbances in the function of the heart. The only differentiating point between syncope and collapse is that in syncope the changes are more sudden and recovery is more rapid. In collapse it is probable that we have

the beginning of the tissue changes of shock, the vicious circles which follow anoxia of the capillary endothelium. Knowledge of the pathological physiology of collapse is hampered by an understandable disinclination to produce this syndrome under experimental conditions in humans. Certain mammals such as rabbits, if tied on a board in the upright position, will go rapidly into collapse and die. Normal human subjects upright and motionless on a tilt table may show the steadily progressing changes previously discussed, which are reversed only by the prone position or by a convulsion following syncope. Were the position further maintained collapse and shock would probably ensue.

In antiquity this human experiment was carried out in the form of crucifixion, and some accurate accounts of the manner of death have come down to us. Apparently bleeding was not an important factor, and in some instances the subjects were tied rather than nailed to the cross. Again, as in the normal human subject on a tilt table, great variability was noted in tolerance. Some died within two or three hours, and this group often exhibited marked thirst which suggests the thirst of shock. It was repeatedly mentioned that when death occurred it was quite sudden, the subject having appeared comparatively strong a few minutes before.

5. *Miscellaneous rarities.* A few very rare types of syncope are worth mentioning because they are so interesting. Cases of polycythemia and obstruction of the superior vena cava may faint at times; cerebral engorgement has been invoked to explain it. Back injuries have been reported to be followed by syncopal attacks, and in such cases loss of tonus in minute vessels of the hands and feet has been demonstrated. Vasodepressor and vagal responses due to central stimulation are seen at times following traumas to the head, either accidental, or purposeful in the form of operations and ventriculograms. A state of collapse is rarely seen following the use of large amounts of procaine for local anesthesia; intravenous barbiturates constitute a highly effective antidote. Syncope has been reported in dissecting aneurysms of the aortic arch, and may be due to mechanical stimulation of the aortic depressor nerve. Syncope of various types may occur rarely with the hyperventilation syndrome.[5] It may be vasodepressor, and due either to the original anxiety producing the hyperventilation, or to anxiety caused by the symptoms of hyperventilation. It may be primarily orthostatic, or it may be hysterical. Prolonged compression of the chest if suddenly released may produce syncope by pooling of the blood in the pulmonary circuit. The Valsalva experiment, a maintained expiratory effort against a closed glottis, may induce syncope by increasing pulmonic pressure to such a degree that the circulation is obstructed.

The Biological Meaning of Common Syncope

Engel and Romano [6] have recently developed a concept of common vasodepressor fainting which embraces the known psychological and physiological

factors involved. They point out that vasodepressor syncope occurs under certain specific circumstances. 1. In healthy people under a wide variety of injuries with or without pain and blood loss. 2. In healthy people under circumstances in which fear must be denied and relative immobility maintained. All the "first time" non-repetitive faints come in this category, the faints that occur on experiencing the first venipuncture, or on witnessing for the first time an autopsy or an operation. 3. In neurotic individuals as a repetitive reaction. From this we see that the bodily changes in fainting represent the physiological concomitants of an emotional state, and that fainting constitutes a generalized reaction to fear of injury, whether real as in the first group, threatened as in the second, or imagined as in the third.

If we now go back to the wider field of biology we find that Charles Darwin, writing in 1872 on the effects of emotion in animals noted a singular paradox. He described the reaction to terror, the trembling, sweating, rapid breathing and tachycardia, and felt that this reaction indicated a preparation on the part of the body for defense. But he also noted certain contradictory manifestations—loss of muscle strength, loss of sphincter tone, prostration and actual fainting.

Walter Cannon's classical work on the physiological concomitants of emotional states has substantiated and expanded Darwin's observations. He demonstrated experimentally that under conditions of terror the organism was prepared for intense physical effort by basic primitive neuro-muscular and neuro-vascular reflexes. But he, too, recognized contradictory manifestations, and showed that an emotion such as terror may not only stimulate, but may also inhibit and depress. Thus an animal may be paralyzed with fear. Engel and Romano feel that it is this biological contradiction that supplies the key to the understanding of common vasodepressor syncope.

We should now be able to take all the premonitory signs of common fainting and fit them neatly into two groups, those due to stimulation and those due to inhibition. But we are at once defeated in such an attempt because homeostatic reflexes provide immediate compensatory reactions. Thus are we to consider pallor a purposeful reaction to prevent bleeding from wounds, or an effort to compensate for undue vasodilation? In general, however, we can consider that stimulation provokes the tachycardia, sweating, increased blood supply to muscles and increased respiratory rate, whereas inhibition provokes the diminished muscle tone and strength, the sudden drop in pulse, and the immobility which contributes to the fall in blood pressure.

We have talked a good deal about the biological response to terror. People who faint usually experience only mild anxiety, rather than fear or actual terror. What has become of the terror, and why do relatively innocuous situations call forth in the human a biological response to terror?

Psychoanalytical investigation of normal people has shown the existence of a very extensive unconscious mind, harboring all sorts of strong emotional

feelings, including fears of a fantastic nature. Such fears are left over from infancy and childhood, but they are in no way diminished by the passage of years. This is in striking contrast to the consciously remembered fears of childhood, which tend to diminish as we grow older and come to understand our environment better. If you will let me substitute shoes for fears, it is as though we carried with us throughout our lives, in a special compartment under lock and key, all the outgrown shoes of childhood. The weight of such a load would constantly affect our movements in any direction. This normal load of unconscious fears may be greatly accentuated in some people, and through association may become capable of being stimulated by relatively harmless situations. The individual is not aware of these unconscious terrors, but his autonomic nervous system is, and it responds just as though the terrifying situation existed in actuality rather than in fantasy.

In the case of the first time fainter the novel situation is enough to mobilize the unconscious fear of injury. Subsequent familiarity minimizes the anxiety and the surge of primitive fear no longer occurs. In the neurotic repetitive fainter, however, the underlying fear of injury is so intense that the same procedure, such as venipuncture, will provoke the reaction over and over again.

We have now seen the animal responding to terror with physiological preparations for fight or flight, and we have uncovered the missing terror in these situations in which the human shows a similar physiological response. But why is this purposeful physiological reaction annulled by inhibitory mechanisms?

A perception of the impossibility of escape seems to be a factor. In the human several more or less conscious feelings combine to make escape appear impossible. Consider our subjects. Characteristically, they are men, often big strapping ones, and they are all of course very brave. This fact, plus their reason, plus long years of social training, defeats any such absurdity as fleeing from or fighting a technician with a syringe. Thus a situation is encountered which, by association and due to unconscious sensitization, results in extreme unconscious fear of injury, together with the physiological concomitants of such fear. Appropriate action is unthinkable, and escape therefore impossible. Let me remind you again that if action in the form of exercise is taken the changes tend to be reversed.

But the question has been answered only partially. Awareness of the impossibility of escape might contraindicate effort, but why should it produce actual inhibition? A reaction so crippling to the mechanisms of defense is in striking contrast to the amazing devices developed by nature for self-preservation. At least an attempt to escape would seem more purposeful. In conclusion one can only guess that the victim, apparently unable to escape, and overwhelmed by fear, finds it preferable to lose consciousness rather than to continue to perceive the danger.

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THE ASSOCIATION OF CAPILLARY SCLEROSIS WITH ARTERIOSCLEROSIS AND PHLEBOSCLEROSIS; ITS PATHOGENESIS AND CLINICAL SIGNIFICANCE *

By Eli Moschcowitz, *New York, N. Y.*

This contribution represents a study of the lesions of the capillaries in organs in which either the main arterial trunk or veins reveal sclerosis. In the lung, pancreas and kidney the vascular lesions show arteriosclerosis; in the liver and spleen, phlebosclerosis. In the former, the capillary lesions are affected by forward intravascular pressures, in the latter by backward pressures. In previous publications [1, 2, 3] I tried to show that prolonged normal intravascular pressure is the dominant conditioning factor in the production of arteriosclerosis and phlebosclerosis and that these lesions come earlier and are intensified under the influence of its increased gradient, hypertension. Likewise the capillary lesions which we term "capillary sclerosis," are most prominent in conditions in which prolonged arterial or venous hypertension exists. Capillary sclerosis bears so many of the morbid anatomical attributes of arteriosclerosis or phlebosclerosis that it represents a veritable vascular sclerosis "en miniature." Indeed the almost constant association of capillary sclerosis with sclerosis of the larger vascular trunks within an organ enables one to predict that when arteriosclerosis or phlebosclerosis is present, the capillaries will show sclerosis and vice versa. For the combined lesions, the term arterio- or venocapillary sclerosis appears applicable. Although the capillary lesions of many of the parenchymatous organs have been described repeatedly, observations are singularly silent on their significance, their relation to sclerosis of the tributary vascular trunks and to pressure changes. The capillary changes of the following organs subject to intravascular hypertension will now be described: (1) lungs; (2) pancreas; (3) kidneys; (4) liver; (5) spleen.

1. Lungs. Normally the capillaries of the uninjected and collapsed lung are hardly visible and one may recognize them only as occasional narrow slits in the wall of the alveoli slightly larger than the contained erythrocyte. The wall of the alveolus is narrow, uniform in thickness, and, with the exception of a bulge of the lining epithelium the alveolar lining is smooth. The wall of the alveolus consists of an alveolar basement membrane and a capillary basement membrane and between the two a sparse fibrillary connective tissue network with an occasional mesenchymal cell. The only anastomotic channels between the pulmonary and greater circulation are capillaries communicating between the alveolar capillaries and the capillary bed of the bronchial arteries, so that the circulation within the lung is practically a closed one.[26] I have

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found sclerosis of the pulmonary capillaries only when gross arteriosclerosis of the pulmonary vessels is observed. In previous papers [2, 3] I have tried to show that gross arterosclerosis of the pulmonary vessels only occurs under conditions in which a hypertension of the pulmonary circulation can be predicated. These are in the order of frequency, mitral disease and especially mitral stenosis, prolonged congestive failure, emphysema, extensive pleural adhesions, marked diminution in lung volume from whatever cause, certain cases of marked scoliosis, open ductus Botalli and communications between the right and left heart (but only when the shunt is from left to right). I have not observed arteriosclerosis of the pulmonary vessels under any other conditions. The independence in incidence between gross arteriosclerosis of the greater and pulmonary circulation, and the invariable sequential relationship of sclerosis of the pulmonary artery to hypertension of the lesser circulation affords to our view the strongest support for our contention that the largest conditioning factor in the production of arteriosclerosis is intravascular tension. The independence in the incidence of arteriosclerosis in the two systems is in all probability due to the fact that the pressure in the pulmonary artery is only one sixth that in the aorta. It is significant that, even though a hypertension of the pulmonary circulation never approaches that of the normal intrabrachial pressure an arteriosclerosis of the pulmonary artery may arise. It is well to consider that it is not the height of the pressure, but rather the duration that determines the presence or absence of the arteriosclerosis. This becomes manifest in correlating clinical data with the anatomical findings.

In the earliest phases of capillary sclerosis, the alveolar wall appears beaded. The capillaries are distinctly dilated and the basement capillary membrane is thickened (figure 1). In cross section, the capillaries bulge into the alveolar space. In more advanced phases the dilatation of the capillaries and the thickening of the capillary basement membrane become more pronounced so that the alveolar wall becomes much thicker than normal and the beaded appearance becomes more pronounced. The capillaries now contain as many as five or six erythrocytes instead of one (figure 2). In this stage, one notes a profound increase in the connective tissue content of the alveolar wall, this increase consisting almost entirely of the extensive thickening of the capillary walls. In a later stage, the connective tissue content of the alveolar wall becomes excessive (figure 3). The connective tissue is cellular, the walls of the alveoli become much thickened and there is a corresponding narrowing of the alveolar spaces, accounting in a large measure for the diminution in vital capacity in cardiac disorders. In many areas hyalinization of the capillary basement membrane is apparent. The capillaries in this stage have become to a large extent obliterated. In the terminal stage the connective tissue transformation of the alveolar wall is so great that the alveolar space becomes but a narrow chink, and the lining epithelium becomes cylindrical in appearance, as in the embryonal lung (figure 3). Capillaries are almost entirely absent, the only vessels persisting in these areas

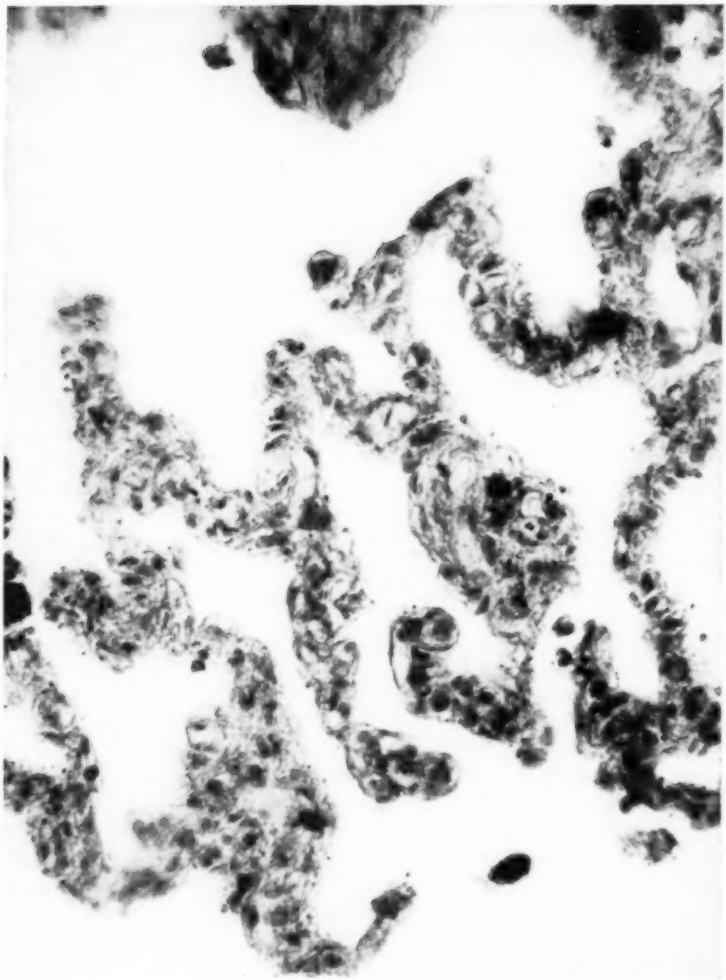

FIG. 1. Early phase of capillary sclerosis. Lung from case of mitral stenosis, showing beaded appearance of alveolar wall due to dilatation and thickening of capillary walls.

being the greatly sclerosed arterioles and arteries. These changes are commonly seen in lungs that have been infarcted, but infarction is only a lesser factor in the production of an increase in connective tissue. One can note in the immediate vicinity of such areas profoundly sclerotic arterioles with the lumen almost obliterated by internal thickening. Undoubtedly, therefore,

diminution in blood supply is in a large measure responsible for the increase in connective tissue.

These marked changes have been confirmed by von Jeddeloh [4] and Parker and Weiss. [5] Parker and Weiss describe in addition changes in the arterioles similar to those described in the kidney in malignant hypertension.

The dilatation, the thickening of the walls, the hyaline changes and the connective tissue proliferation represent morbid changes which are part and parcel of true arteriosclerosis, and which I believe can be viewed as the result of a mechanism identical with that which is responsible for the development of arteriosclerosis. Obviously reduplicating of the elastica cannot occur, since the elastic layer is wanting in capillaries. We have tried to show that atheroma, calcification and mucoid degeneration are only secondary or facul-

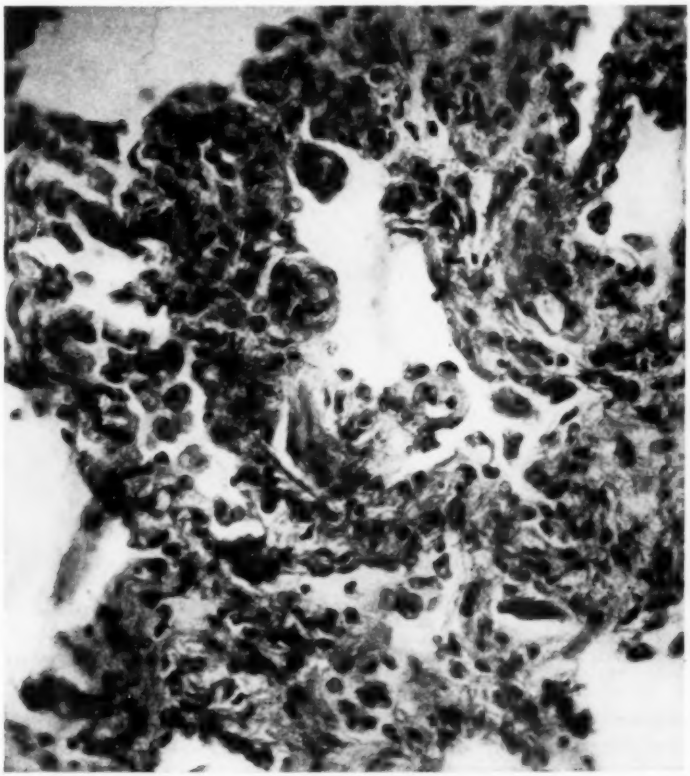

FIG. 2. Later phase of capillary sclerosis. Lung from case of mitral stenosis showing greater thickening of alveolar wall. Walls of individual capillaries greatly thickened and some are hyalinized. Note capillary bulging within the lumen of the alveolus in the center.

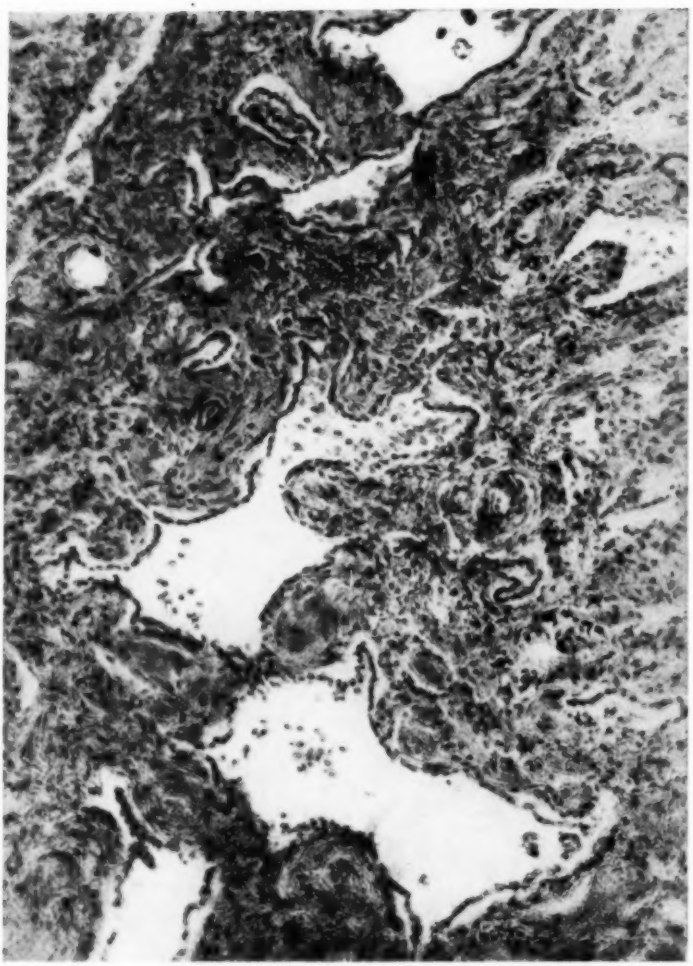

FIG. 3. Terminal phase of capillary sclerosis. Lung from case of mitral stenosis. Note intense sclerosis of alveolar walls with almost complete obliteration of the capillary bed. Also note reversion of the morphology of the lung to the embryonal type.

tative lesions in arteriosclerosis.[6] In other words, the changes in the capillaries of the lung in hypertension of the pulmonary circulation represent an extension of the vascular sclerosis of the grosser arteries of the lungs.

That these lesions when found in mitral stenosis are not the result of rheumatic fever is shown by the identity of the capillary lesions in hyper-

tension of the pulmonary circuit due to other causes, congenital cardiac lesions, for instance.

Teleologically one may deem the capillary sclerosis as a compensatory mechanism, at least in its earlier stages. The widening of the capillaries permits a greater flow of blood to counteract the decreased rate of capillary flow consequent upon the increase of peripheral resistance, thus permitting a wider surface for the diffusion of oxygen. The thickening of the capillary wall is compensatory to the increase in intracapillary pressure, thus obviating possible rupture of the delicate basement membrane. Both these compensatory mechanisms accord with the laws of Thoma on the growth of blood vessels. [7] In the later stages these morbid processes overshoot the mark, and bring in their train consequences that lead to decompensation. We refer particularly (1) to the progressive diminution in the calibre of the alveolus which results in diminution in vital capacity; (2) to the progressive thickening which interferes with the exchange of oxygen; (3) to the obliteration of the capillary bed which increases the peripheral resistance and (4) to the sclerosis of the arterioles which may lead to thrombosis or rupture.

2. Pancreas. The capillary sclerosis is seen in the islands of Langerhans. These are glomerular-like structures consisting of a network of capillaries between which are the secreting cells. The diameter of the capillaries is somewhat wider than the interacinar capillaries.[8] The capillaries have a thin basement membrane and a delicate endothelial lining similar in structure to the hepatic sinusoids but without Kupffer cells. The islands are richly supplied with blood which sometimes comes from an efferent arteriole or from the neighboring interacinar capillaries. There is a rich anastomosis between the capillaries of the islands and those of the interacinar rete. [9]

Capillary sclerosis of the pancreas is best studied in diabetes mellitus. Opie, [10] in his classical monograph, describes hyaline deposits of the capillary wall, which according to Warren [11] are due to the production of intercellular substance by fibroblasts and possibly by the endothelial cells. The hyalin is not always uniform in distribution, but occurs as scattered groups of irregular rounded globular masses, with compressed island cells between. Often the island is completely hyalinized (figure 4). Opie also found that hyaline degeneration of the islands is often accompanied by interacinar fibrosis of varying degrees, and nearly always with arteriosclerosis of the grosser vessels of the pancreas.

Cecil [12] found lesions of the islands in 88 per cent of diabetics. As a rule, the majority of islands are affected. In accord with Opie, Cecil found that the hyalin is deposited along the walls of the capillaries of the islands. Cecil also describes fibrous sclerosis of the capillaries (figure 5). In these islands, the fibrous wall of the capillaries is definitely increased in thickness, converting the vessels into coarse septa which extend in from the capsule. Of 76 cases of diabetes mellitus, 42 showed sclerosis of the capillaries, while 27 showed hyaline changes. In many capillaries both hyaline degeneration and

sclerosis were associated. Cecil found arteriosclerosis of the main vessels of the pancreas, in all but seven of 86 cases of diabetes mellitus.

Warren's [11] description of the changes in the islands of Langerhans follows Opie's and Cecil's closely. He found hyalinization in 96.6 per cent of diabetics over 40 years of age. He found fibrosis less frequently than Cecil,

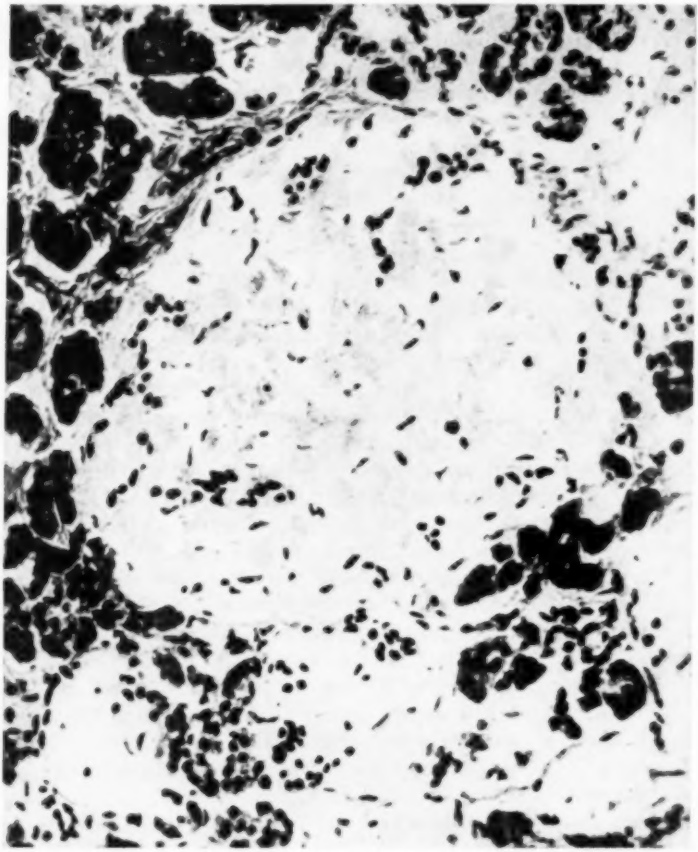

FIG. 4. Island of Langerhans showing complete hyalinization of capillary walls.

in 27 per cent. Hyalin deposits and sclerosis occasionally occur in different islands or even along the same vessel. Fibrosis also tends to occur in older individuals, although of the lesions found in young people, it is one of the more frequent. He finds that arteriosclerosis of the pancreatic vessels is always accompanied by interacinar and interlobular fibrosis. That island

lesions are not a specific property of diabetes is shown by his finding of 2 per cent hyalin and 7.5 per cent fibrosed islands in the pancreas of non-diabetics. When the process becomes sufficiently marked to destroy the secreting cells of the islands, diabetes will develop.

The vascular pattern in the pancreas, namely capillary sclerosis associated practically always with arteriosclerosis, is precisely what we have described

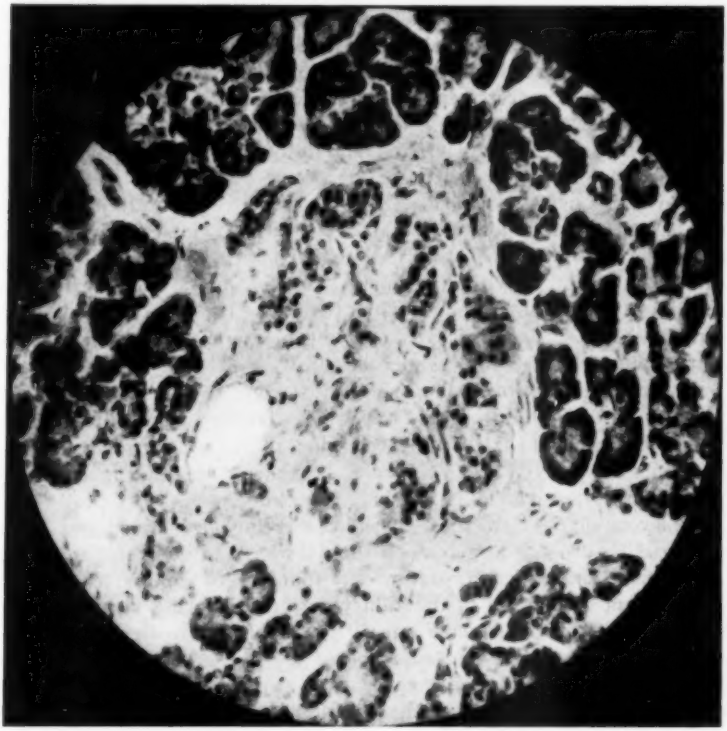

FIG. 5. Island of Langerhans showing fibrosis of capillary walls. (From Joslin, Root, White and Marble, Treatment of Diabetes Mellitus, 1940, Lea and Febiger, Philadelphia.)

in the lung. The genesis of the lesion, however, cannot always be ascribed to hypertension of the greater circulation, since hypertension is present in diabetes in only 52 per cent according to Joslin [13] and 39 per cent according to Kramer. [14] The probable reason why diabetes is not more common in hypertension is because the capillary circulation in the islands possesses a comparatively wide shunt to the interacinar capillaries thus minimizing the insular intracapillary pressures. The capillary circulation is not therefore as closed as in the lung. It might be argued that the arteriosclerosis is the

result of diabetes. The common association of arteriosclerosis and diabetes is often cited as proof of such a causal relation, but as I pointed out before [15] diabetes cannot be a cause of arteriosclerosis, because in diabetics, uncomplicated by a condition that might cause hypertension of the pulmonary circulation (vide above), arteriosclerosis is always present in the aorta, while the pulmonary artery is free.*

While the cause of the capillary sclerosis in the pancreas cannot always be ascribed to a hypertension of the greater circulation, we believe, as in the kidney, that a prolonged normal intravascular tension is responsible. This accounts for its extraordinary frequency in the later years of life. It may therefore be termed a decrescent capillary sclerosis.

Why hyaline degeneration is so much more common in the capillary sclerosis of the islands of Langerhans than in the lung or liver is not clear.

3. Kidney. The glomerular tuft fits closely to the capsule of Bowman and consists of a whorl of capillaries which are composed of a thin connective tissue basement membrane and a fairly conspicuous flat endothelial lining which is not continuous. The surface of the glomerular tuft is also covered by flat endothelium, which is continuous with that lining the Bowman capsule. The capillary blood supply comes through an afferent arteriole which penetrates the capsule and is carried away by an efferent vein. There are no communications between the glomerular tufts. [16] The capillary circulation within the glomerular tuft is therefore a closed one.

Compared to the large number of studies on the changes in the gross vessels of the kidney in essential hypertension, those on the capillary changes have been comparatively few. There is a very wide range in the extent and damage in hypertensive disease, varying from kidneys with practically intact glomerular capillaries [17] to those in which the damage is ubiquitous. This wide variation depends largely upon the duration and degree of the hypertension since Castleman and Smithwick [18] found no or slight arteriosclerosis in 53 per cent of biopsies of the kidney performed during sympathectomy. The average age of the patients was 39 years. In the malignant phase the damage is intense and widespread.

In a study of 30 kidneys removed from patients dying from uncomplicated hypertension, I found changes identical with those described in the lung in hypertension of the pulmonary circulation. There is dilatation of the capillaries, but the dilatation is not as a rule as wide as in the lung, probably because of the denser environment of the capillaries within the glomerular capsule and renal parenchyma, as compared to the alveolar space. The basement membrane is thickened and very frequently shows hyaline change (figure 6). Most observers [19, 20] regard the hyalinization as the result of

* Regrettably many pathologists employ the terms arteriosclerosis and atherosclerosis interchangeably. That atheroma is only a facultative lesion of arteriosclerosis is proved by the observation that it is lacking in the true hyperplastic arteriosclerosis, characterized by proliferation of the intima and elastica. In arteriolosclerosis, atheroma is mostly absent. In phlebosclerosis a lesion morphologically and pathogenetically identical with arteriosclerosis, atheroma only rarely occurs.

extension of the hyaline deposit from the afferent vessel or upon ischemia consequent upon the sclerotic narrowing of this vessel, but Jaffe [21] showed by serial sections that there is often no connection between the hyaline of the glomerular capillary and the afferent vessel. The hyaline is often found only on the distal end of the capillary. In the later stages, the glomerular tuft shrinks due to sclerotic contraction. When narrowing and/or occlusion of the afferent vessel occurs, severe sclerosis of the glomerular capillaries is readily explainable. The lesions are like those of an infarct. There is often an irregular distribution of these capillary lesions, and some capillaries may be involved while others are intact.

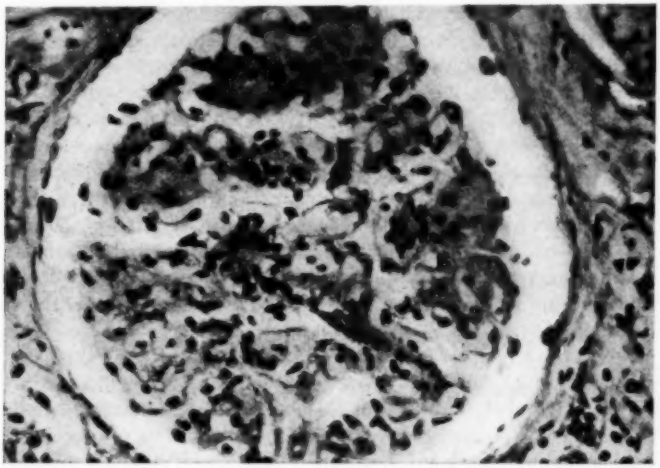

FIG. 6. Glomerulus from a case of advanced hypertensive disease showing thickening of capillary walls, some with hyalinization.

McGregor's [22] findings accord with those we have described. She computed the percentage of involved glomeruli in those dying of uremia as 47 per cent, in those dying of myocardial failure or coronary disease as 33 per cent and in those dying of cerebral accidents as 24 per cent. In severe chronic glomerular nephritis with hypertension, McGregor also found glomerular sclerosis in a small proportion. That hypertension was the dominant cause of these lesions is shown by the fact that in individuals dying between the fifth and eighth decade, who did not present hypertension, 96 per cent of the glomeruli were normal. Nevertheless, in these an occasional hypertensive glomerulus was found, showing that in the kidney also, as in the pancreas, a decrescent capillary sclerosis occurs.

In the malignant phase of essential hypertension there is an exaggeration of the capillary sclerosis. Klemperer and Otani [23] describe collapse of the capillaries, degenerative changes in the capillary wall varying from hyaline

droplet degeneration to complete necrosis, endothelial proliferation, adhesion of the capillary tufts and occasionally, leukocytic accumulation. These changes are usually associated with necrosis of the afferent arteriole and may occur not only in essential hypertension but also in chronic glomerulo-nephritis. There appears to be a fairly consistent relation between arteriolar necrosis and prolonged excessive diastolic pressures.

In my experience, capillary sclerosis of the glomerulus is practically always associated with arteriosclerosis of the renal vessels. Why the brunt of the hypertension is thrust on the renal arterial vasculature rather than on the remaining portions of the arterial tree of the greater circulation is a problem that still awaits solution.

As in the lung and liver the early dilatation of the glomerular capillaries and thickening of the basement membrane may be viewed as compensatory to the hypertension. In the later stages the severe sclerosis undoubtedly contributes to a progressive renal insufficiency, depending on the intensity and extent of the sclerosis. Nevertheless, it is difficult to appraise the functional consequences for a number of reasons. First: the compensatory mechanisms. The thickened capillary walls will reduce the filtration rate so that certain substances, especially the phosphates, sulfates and the nitrogenous products of metabolism will be retained; but the acidosis and the azotemia are offset by the diminution of water absorption by the tubules, permitting a greater water excretion, and a lowering of the specific gravity of the urine. When this attains 1010 which is that of the glomerular filtrate, the tubules can no longer compensate by this mechanism and these substances begin to accumulate in the blood. Second: the extra renal factors, especially cardiac. The frequency of cardiac manifestations in hypertensive disease, whether essential or associated with glomerulo-nephritis, need not be emphasized. That these affect glomerular functions is evidenced by the proteinuria and occasional azotemia which arise in cardiac failure. Furthermore, a reduction in blood pressure, from a coronary thrombosis for instance, will cause an oliguria or anuria and again an azotemia. In the terminal phases, especially when the capillary sclerosis is excessive and is associated with necrosis, proteinuria and hematuria are the rule.

4. Liver. The hepatic sinusoids possess a delicate basement membrane lined by a sparse endothelial layer and the Kupffer cells which have an independent function.[16] The sinusoids are occupied by blood which arises from the terminal branches of the hepatic artery and the portal vein which course through the interlobular spaces. According to Wakim and Mann[25] there are arteriovenous connections between these two terminal branches. The sinusoids drain into the central veins and thence into the hepatic veins.

In a previous publication[21] I tried to show that capillary sclerosis around the central veins of the hepatic lobule was invariably associated with dilatation and phlebosclerosis of the hepatic veins and that the summation of this process represented the conventional type of cardiac cirrhosis. Phlebosclerosis of the hepatic veins is an exquisite example of the causal relation of pro-

longed venous pressure to the production of phlebosclerosis, since it is found only in conditions associated with sustained hypertension of the hepatic circulation, notably in tricuspid disease and in constrictive pericarditis. The dynamics of the circulation whereby such a sustained venous hypertension is attained have been previously outlined. [15] While cardiac cirrhosis is associated with dilatation and phlebosclerosis of the hepatic veins, the latter lesion may occur unassociated with a cardiac cirrhosis, thus differing from the invariable mutual association of the alveolar capillary sclerosis and sclerosis of the pulmonary artery. We ascribe this to the circumstance that in the liver there is a wide release to the intracapillary pressure due to the communications of the capillaries with the portal radicles while in the lung there is only a slight communication between the capillaries of the lung and the capillaries of the bronchial arteries.[26] This accounts for the infrequency of cardiac cirrhosis as compared to the frequency of the analogous changes within the lung.

The observation that hepatic vein sclerosis bears a definite relation to increased venous pressure furnishes a clue to the pathogenesis of cardiac cirrhosis. Cardiac cirrhosis is conventionally viewed as a replacement fibrosis around the central vein, that is, as a condensation of the reticulum, sequential to the capillary dilatation and atrophy of the adjacent liver trabeculae. That the sclerosis does not represent a mere condensation of the reticulum is shown by the fact that the reticulum fibers are both hypertrophied and increased. [27, 28, 29] We believe that the sequence of events is precisely comparable to the capillary sclerosis that we have described in the lung. In the earliest phase there is dilatation of the central vein and the sinusoids in the central portions of the lobule. The trabeculae are correspondingly narrowed. In the midphase one notes a thickening of the connective tissue wall of the sinusoids in these areas, most marked in the sinusoids immediately around the central veins and becoming less and less toward the periphery of the lobule (figure 7). This represents the conventional lesion of passive congestion. The dilatation of the sinusoids may be so excessive that the trabeculae become exceedingly thin. In the latest stage, the central vein and adjacent tributary capillaries become completely obliterated by fibroblasts. To what extent the fibrosis around the central veins represents a replacement phenomenon is difficult to determine. In very advanced instances one may even note occasional hyalinization of the thickened walls of the sinusoids. In passing, one notes frequently in advanced cases, compensatory hyperplasia of the liver trabeculae around the intact portal spaces.*

We again observe the remarkable parallelism both morphologically and pathogenetically between the morbid process in the lung and in the liver, and to our view, the process in the liver may only be ascribed to the increased capillary pressure. Under normal circumstances the pressure in the inferior

* We have observed a comparatively high incidence of periportal sclerosis associated with cardiac cirrhosis. Katzin, Waller and Blumgart [30] found such a sclerosis in 23 per cent of patients dying in congestive failure.

vena cava is negative and the probability is strong that the pressure within the hepatic veins is also negative or close to zero. To what elevation the pressure in these vessels attains under the abnormal conditions associated with a hypertension of the pulmonary circuit it is impossible to say. But

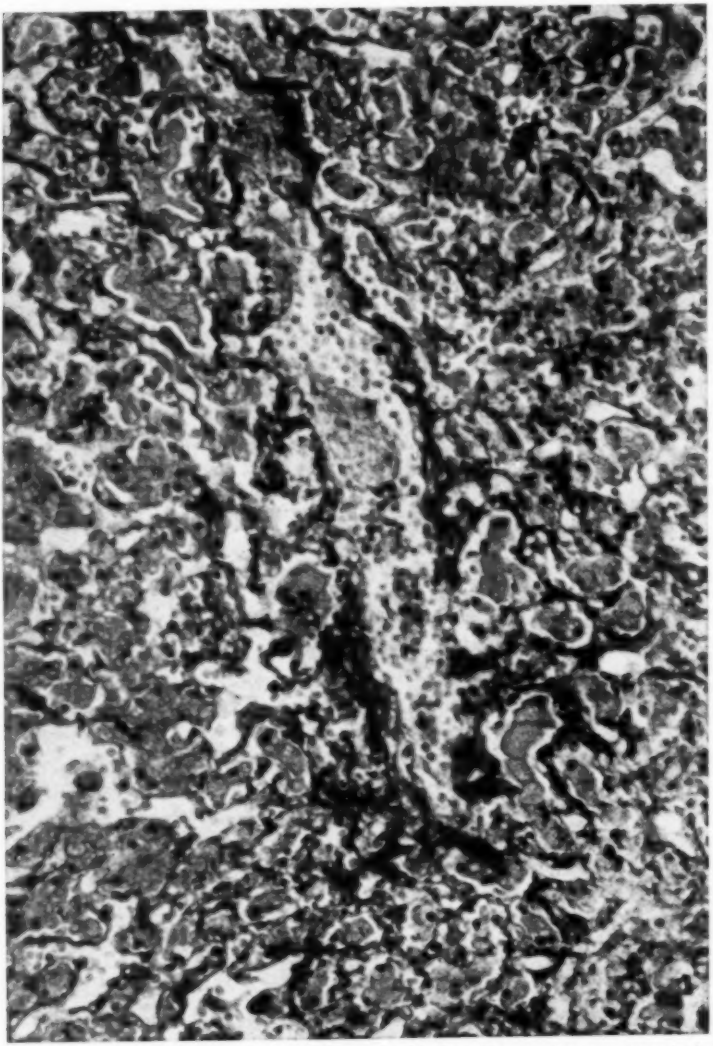

FIG. 7. Liver from cardiac cirrhosis showing sclerosis of capillary walls around central vein.

there is no doubt that the dilatation of the hepatic veins and their tributaries is an important element in compensating for the increased pressure within the right cardiac chambers, thus acting as a reservoir. Inasmuch as the pressure in the cubital veins is more or less proportional to the pressure within the right heart, this test should serve as an approximate indication of the pressure within the hepatic veins. During attacks of congestive failure the rise is transient and does not lead to phlebosclerosis of the hepatic veins. In tricuspid disease and especially in constrictive pericardium, the venous pressures are notoriously persistent. The site where the sinusoidal capillary flow meets its first resistance is at its entrance into the central vein and it is precisely here that the fibrosis begins.

The earliest dilatation of the sinusoids, concomitant with the dilatation of hepatic veins, may be viewed as compensatory to the increased resistance encountered by the flow of blood in the capillaries around the central vein, thus fulfilling one of the functions of the liver, namely, as a blood reservoir. This is observed clinically by the enlargement of the liver during the earlier phases of congestive failure when the venous pressure is elevated and its recession when compensation with reduction of venous pressure is restored. Before fairly extensive fibrosis occurs, the other functions of the liver show hardly any impairment. When fibrosis supervenes, decompensating mechanisms ensue and definite impairment of liver function is observed.

The reservoir function of the liver is diminished. The organ no longer enlarges and recedes during periods of congestive failure and under such circumstances, dependent or general anasarca develops due to the prolonged maintenance of increased pressure in the venous segment of the systemic capillaries. In constrictive pericarditis, where a prolonged venous pressure is usually maintained for years, anasarca is always associated.

An extensive fibrosis leads to hypertension of the portal circuit. This is manifest in the morphological evidences of "congestive splenomegaly." These evidences will be discussed under the next heading. Clinically, the most striking example is exemplified in the pericarditic pseudocirrhosis described by Pick, which we believe is the result of prolonged maintenance of a high portal venous pressure.

Hepatic insufficiency. The liver has a wide safety factor so that very extensive liver damage must occur before evidences of hepatic insufficiency arise. Nevertheless, in congestive failure, hyperbilirubinemia, increased urobilogen in the urine and augmented lactic acid in the blood sometimes are observed.[31] Jolliffe [32] with various tests found impairment of liver function in 15 of 16 patients. With the bromsulfalein test, he found impairment of excretion in 12 of 16 patients; Cantarow [33] in 14 of 42.

5. *Spleen.* The terminal branches of the splenic artery as they penetrate the splenic pulp are extremely narrow and consist of endothelium supported by a few longitudinal fibers and elongated spindle cells. These vessels, although termed capillaries, are wider and the walls are more solidly constructed than the capillaries of other organs. It has been amply demon-

strated that these terminal vessels end in a funnel shaped dilatation, the ampulla of Thoma, the walls of which show stomata. The splenic sinuses, the walls of which represent the beginning of the splenic venous system, unlike the veins, are not lined by a flat vascular endothelium but by narrow cells parallel to the long axis of the vessel, with prominent nuclei that bulge into the lumen. The walls of the splenic sinuses are not continuous but like the ampulla of Thoma are perforated with numerous stomata and it is through these stomata that the free blood cells lying within the meshes of the pulp cords flow into the veins. The sinuses unite to form the pulp veins which enter the trabecular veins. The manner whereby the blood flows between the ampulla of Thoma and the splenic sinuses has given rise to controversy as to whether the circulation in the spleen is an open or a closed one. The weight of modern observation is overwhelmingly in favor of an open circulation.[34, 35, 36, 37] The evidences of an open circulation derived from the observation and interpretation of histologic preparations have been convincingly confirmed in the living animal with the aid of the quartz rod illumination technic by MacKenzie, Whipple and Wintersteiner.[38] According to their observations, the blood from the ampulla of Thoma flows directly into the meshes of the pulp reticulum comprising the pulp or Billroth cords which lie between the sinuses. According to MacKenzie and his coworkers, the pulp spaces in the relaxed spleen measure 6 m. in width but the diameter of dilated ones is 16 m. This potential dilatation together with that of the sinuses affords a measure of the distensibility of the normal spleen and accords with the observation of MacMichael[39] who found that the spleen can be distended to about three times its normal size. The blood then flows from the pulp spaces into the sinuses through the stomata and thence to the trabecular veins which unite at the hilus to form the splenic vein. The pulp spaces are the only means of communication between the arteries and veins within the spleen and represent therefore the analogues of the capillaries in other organs that have a closed circulation.

In a recent study[40] of the pathogenesis of "congestive splenomegaly" in 86 cases in which a cause for a hypertension of the portal circulation was demonstrable (all but two were autopsy cases) I was able to show that the splenomegaly was the result of a progressive veno-capillary sclerosis. The finer morphology of these spleens was studied from the biological point of view and the changes were traced from the earliest to the most mature phase. In this we were aided by the simultaneous study of an accessory spleen in a few cases. The evolution is identical no matter what the cause of the portal hypertension may be. The earliest stage is seen in fresh red thrombosis of the portal or splenic vein. The spleen is large, approaching that of extreme distensibility of the normal organ (450 gm.). The spleen is so distended with blood that the sinuses are not visible. The pulp cords of Billroth are broken up; the pulp cells are normal but widely dispersed. In the succeeding stage when the thrombus has become gray and adherent, the sinuses again become visible but are widely distended and the lining endo-

thelium is flattened. The pulp cords are narrow and the pulp spaces are distended with erythrocytes. The cells of the pulp are not as dispersed and remain normal in appearance (figure 8). The spleen has shrunk somewhat. In the next stage when the thrombus has become partially organized, the pulp

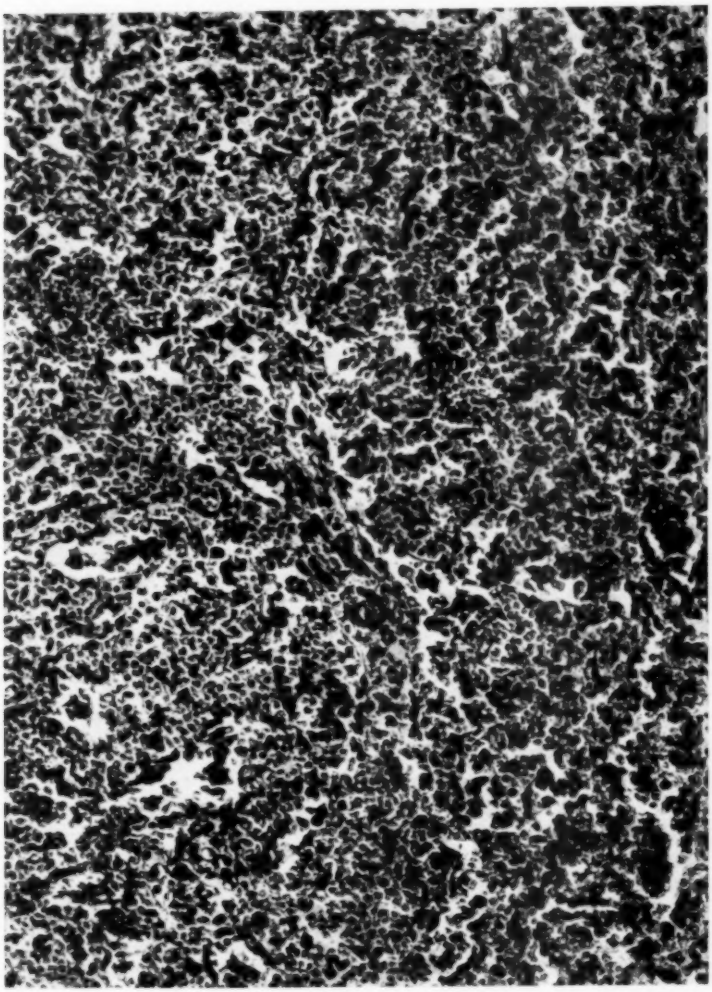

FIG. 8. Spleen from case of organizing thrombus of portal vein showing Billroth cords filled with erythrocytes between which are the sinusoids with flattened endothelium. Earliest phase of "congestive splenomegaly."

cords begin to widen, the pulp cells increase and have undergone a fibroblastic change. The pulp spaces show an appreciable diminution in erythrocyte content. Well defined sinuses appear which are still dilated and the lining endothelium is no longer flat. When the thrombus has become firm and well organized, the pulp cords become still wider and the pulp spaces contain fewer erythrocytes. The pulp cells now show not only a fibroblastic change but they are increased. The sinuses are abundant, less dilated and the fibrillar reticulum around the sinuses is thicker and denser. When the thrombus has become completely fibrous, the pulp cords are wide and the pulp spaces contain only a minimal quantity of blood. The pulp cells become predominantly fibroblastic and the sinuses show extensive hyperplasia (figure 9). The spleen is now much larger than normal. When the thrombus becomes so completely organized as to be termed "cavernous transformation," the maturation of the process almost attains its maximum. The pulp cords become sclerosed and canalized and the pulp spaces contain only a minimal number of erythrocytes. The pulp cells are now all flat fibroblasts. The sinuses are sharply defined and definitely hyperplastic. The lining endothelium is unusually prominent (figure 10). The spleen is now huge, averaging around 1000 gm. The maximum phase was noted in one spleen, the result of cavernous transformation of the splenic vein. Here the pulp cords were completely transformed into firm fibrous connective tissue, so that in many areas the containing pulp spaces appeared bloodless. In this organ the splenic circulation had been converted from an open to a practically closed one (figure 11).

All these stages except the terminal were noted in spleens in hypertension of the portal circulation no matter what the origin. The maladies studied were the following: portal, biliary and toxic cirrhosis; the cirrhosis associated with hemochromatosis and schistosomiasis; acute, subacute and chronic thrombosis of the portal or splenic veins, including cavernous transformation of these veins: cardiac lesions with prolonged failure, with hepatic fibrosis and without: constrictive pericarditis and obstruction of the hepatic veins. The least mature are the acute obstructions of the portal vessels and those in which the portal hypertension is of central or cardiac origin. The latter never achieve a full maturity, in all probability because the hypertension is not sufficiently prolonged, except in constrictive pericarditis. In the latter cases the lesions are correspondingly much more mature. The most advanced lesions occur in chronic extrahepatic vascular obstructions and have been termed "congestive splenomegaly." In between but approaching the latter are the various forms of hepatic cirrhosis and obstruction of the hepatic veins. The morphological differences in all these varieties are quantitative and not qualitative. The largest spleens and the most mature lesions occur in splenic vein obstruction. The proofs that reveal that hypertension of the portal circulation is the dominant factor in the production of these lesions are the following: 1. In portal cirrhosis, in the cirrhosis of schistosomiasis, in the cirrhosis of toxic hepatitis, in chronic thrombosis of the

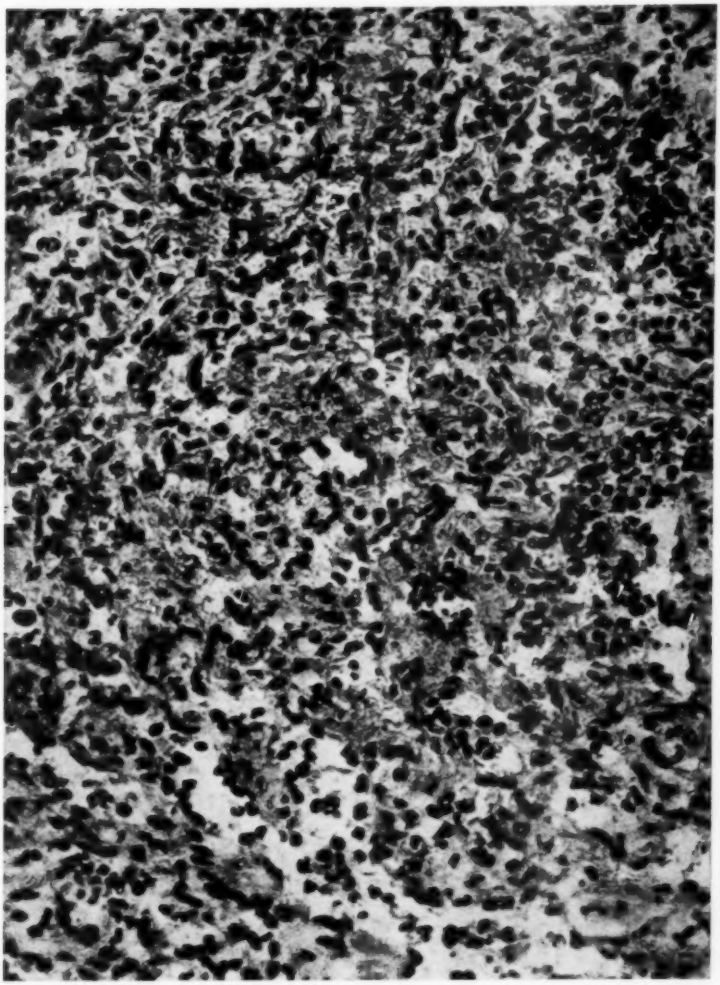

FIG. 9. Spleen from case of constrictive pericardium showing beginning fibrosis and widening of Billroth cords between which are well formed sinusoids with prominent endothelium. Midphase of "congestive splenomegaly."

portal and/or splenic veins Thompson [41] and Rousselot [42] made simultaneous measurements of the pressures within the splenic and antebrachial veins and found the pressure in the splenic vein appreciably greater than in the antebrachial veins, usually about 10 times as high. 2. In constrictive pericarditis, where high venous pressures are consistently maintained, the same changes

occurred in the spleen, although they attained only what may be termed the midphases of the process. 3. In the cases in which an accessory spleen was studied, the lesion was much less advanced than in the main organ. This was undoubtedly due to the much smaller venous tributary, in which the pressure was not quite as elevated as in the main branch. 4. The develop-

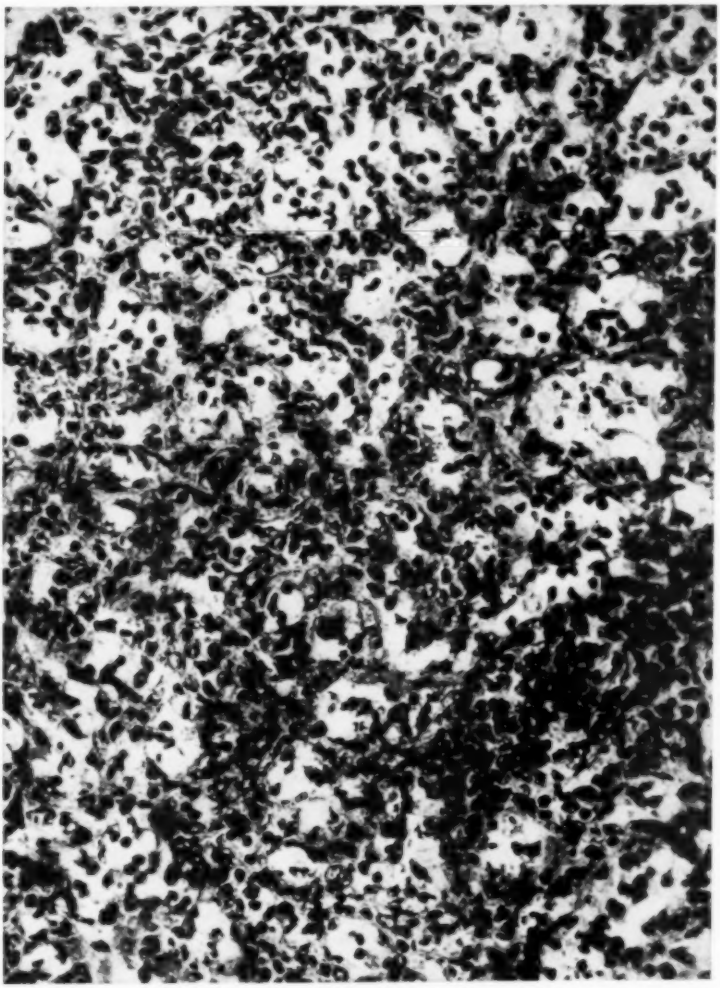

FIG. 10. Spleen from case of cavernous transformation of portal vein showing more advanced fibrosis of Billroth cords and sinus hyperplasia. Late phase of "congestive splenomegaly."

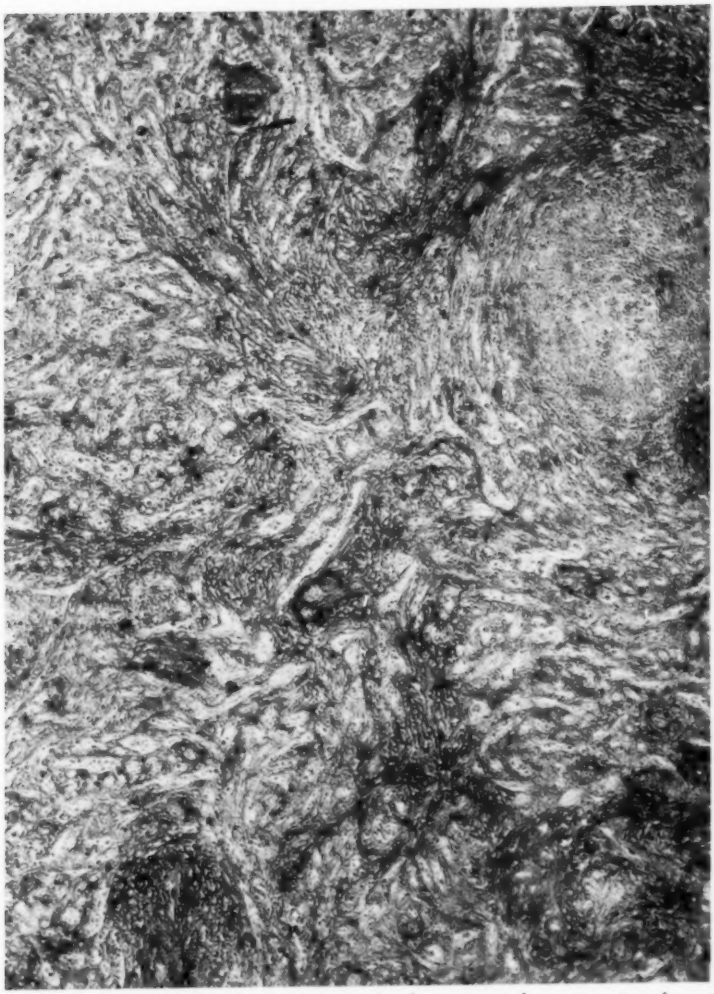

FIG. 11. Terminal phase of portal hypertension from a case of cavernous transformation of the splenic vein. Spleen 24 by 15 by 6 cm. Low power; extensive sinus hyperplasia, mature fibrosis. In this spleen the circulation has been converted from an open into a practically closed one.

ment of a compensatory collateral circulation between the portal and general circulations around the lower end of the esophagus. This occurs only in the intrahepatic and extrahepatic obstructions, but not in the portal hypertension of cardiac origin. In the latter an anastomotic circulation cannot arise be-

cause the venous pressure in the portal and general circulation are presumably equal. A collateral circulation only arises when an area which has been subjected to prolonged venous pressure must divert its blood into an area where normal pressures prevail. 5. The frequent association of phlebosclerosis of the portal vessels. It seems remarkable that the frequency of phlebosclerosis (under the stimulus of venous hypertension) and its morphological similarity to the sclerosis that occurs in arteries was entirely overlooked as a clue to the possibility that portal hypertension was the direct cause of the lesions of "congestive splenomegaly" until MacMichael's study in 1934. But he also held that the same factor that produced the cirrhosis caused the splenic changes. This is hardly tenable in view of the identity of the splenic histomorphology in hepatic cirrhosis and in extrahepatic portal obstruction. The portal veins show thickening of the intima, splitting of the elastica, hypertrophy of the muscular coat and degeneration within the deeper layers with fibrosis. Previously almost every student of hepatic cirrhosis and "Banti's disease" regarded the phlebosclerosis as "primary" and of unknown origin. A number ventured the opinion that it was syphilitic, but without the slightest morphological evidence. The phlebosclerosis is exceedingly common; my own experience is not sufficiently valid to warrant an estimate of the incidence of phlebosclerosis of the portal vessels in hypertension of the portal circulation since the protocols, especially of an earlier date, are silent on this observation; and above all because in the vast majority of instances gross observations and not microscopic study of the veins were reported. Li,[43] however, found that in his cases of hepatic cirrhosis the incidence of phlebosclerosis of the portal or splenic veins was 77 per cent. The probability is therefore strong that a painstaking study of the portal veins in hypertension of the portal circulation would show as high a per cent if not higher.

It is apparent that the peripheral resistance may be anywhere between the heart and the hilus of the spleen. On mechanistic grounds one would presume that, other things being equal, the more distal from the spleen the peripheral resistance, the less the portal hypertension and therefore the less mature the lesions. Such indeed has been found to be the case. But there are other influences that modify the morphological picture profoundly. If the clinical history and the maturity of the splenic lesions are correlated, it was found that, as in pulmonary and hepatic vein sclerosis, the longer the duration of the hypertension of the portal circulation the more mature the lesions. This is also manifest in the marked difference in morphology in acute, subacute and chronic vascular obstructions. Another factor is unquestionably the degree of the portal hypertension. This is indicated by Thompson's [41] observation that the greater the density and distortion of the fibrosis in portal cirrhosis, the greater the splenomegaly. Until systematic studies of portal hypertension at operation are correlated with the maturity of the lesions, no statement can be made concerning the precise effect of the degree of portal hypertension. There is a certain parallelism

between hypertension of the portal and of the greater circulation. In the greater circulation, the most advanced sclerosis of the arteries and of some of the tributary capillaries, notably of the glomeruli, is observed in the "malignant" types in which both systolic and especially diastolic pressures are excessive.

If we view the red pulp spaces in the spleen as the anatomical analogues of the terminal capillaries in organs with a closed circulation, and the very common association of sclerosis of the portal veins, it becomes clear that the later phases of "congestive splenomegaly" represent both in their evolution and morphology a veno-capillary sclerosis, comparable in every way with that we have described in other organs. The progressive sclerosis of the pulp cords of Billroth permits of no other interpretation. The ultimate physiological effects of such a sclerosis will be to convert the circulation within the organ from an open to a more or less closed one and the spleen will lose much of its function as a blood reservoir. What other functions may be compromised awaits future study.

The term "congestive splenomegaly" conventionally adopted at Larrabee's [44] suggestion is not strictly accurate, since congestion is not physiologically synonymous with venous hypertension. The term "portal hypertensive splenomegaly" would be more appropriate. The validity of "Banti's disease" characterized by "congestive splenomegaly" has been entirely discredited as a nosological entity, both clinically and anatomically.

Comment

These five organs in which either arterio- or veno-capillary sclerosis can be demonstrated lend themselves readily to such study because the capillaries can be studied in mass formation, while the tributary arteries and veins are large and the affected capillaries have a more or less closed circulation. Other organs are probably subject to the same influence and such studies we hope to pursue. The probability is strong from the evidences we have submitted that we shall find no or minimal changes in organs that have rich anastomotic outlets for the capillaries. That the systemic capillaries are affected by capillary sclerosis is suggested in the study of the peripheral capillaries in hypertensive disease by the Lombard method, when they are found deformed, tortuous and irregularly thickened.[45]

Summary

Capillary sclerosis is an invariable accompaniment of the general sclerotic process that affects the vascular system. When the main artery of an organ is affected by arteriosclerosis, the distal capillaries reveal capillary sclerosis. This has been demonstrated in the lungs, the pancreas and the kidneys. When the main vein of an organ is affected by a phlebosclerosis, the proximal capillaries also show capillary sclerosis. This has been demonstrated in the liver when the hepatic vein reveals sclerosis and in the spleen when the splenic and portal veins show sclerosis. Evidence has been submitted to

show that arterial and venous hypertension within these vessels is the cause of the sclerotic process. In the pancreas and kidney a descrescent capillary sclerosis, that is unassociated with hypertension, may occur. We have reason to believe that this is the result of prolonged normal intraarterial tension, since it is associated with the decrescent arteriosclerosis of advanced years. A decrescent venocapillary sclerosis is probably impossible, since venous pressures are low and even under abnormal conditions never approach the normal systemic arterial pressures. We have not observed decrescent capillary sclerosis in the lung for the same reason, since the pressure in the pulmonary artery is only one-sixth that within the aorta.

In the organs affected by arteriosclerosis, the distal capillary sclerosis is the result of forward intravascular pressure; in those with phlebosclerosis, the proximal capillary sclerosis is the result of backward pressure. The capillary sclerosis affects the function of these organs to a greater or lesser extent. Teleologically, the early phases of capillary sclerosis represents a compensatory adaptation to the prolonged arterial and venous hypertension. In the later phases, the decompensating effects of the exaggerated phases of the lesions upon the function of each organ have been outlined.

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COMPARATIVE STUDIES ON THE IODINE ABSORPTION OF ANAYODIN, CHINIOFON, DIODOQUIN, AND VIOFORM IN MAN *

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David, Phatak, and Zener, [1] in 1943, published studies made on the toxicity and absorption of Iodochlorhydroxyquinoline (Vioform) and Diiodohydroxyquinoline (Diodoquin) in man. Their studies failed to include Iodoxyquinoline sulphonic acid (Chiniofon) also known as Anayodin or Yatren. Likewise, Diodoquin was not given in its recommended therapeutic dosage; therefore, the blood iodine levels and toxicity were not determined at therapeutic levels. Toxicity studies revealed both Vioform and Diodoquin to be relatively safe drugs since the recommended full therapeutic dosage in the thinnest individual is not over 8 mg. per kg. of Vioform and 30 mg. per kg. of Diodoquin. The lethal dose of Vioform was shown to be 175 mg. per kg. in the guinea pig and 400 mg. per kg. in kittens, and although the lethal dose of Diodoquin could not be determined accurately it apparently occasionally killed guinea pigs or kittens in doses of 50 to 2,000 mg. per kg. but showed its greatest number of deaths at 300 mg. per kg., killing four out of 10 guinea pigs at this level.

The postmortem histologic changes showed liver damage and were similar in type to chloroform poisoning as shown by David, Johnstone, Reed, and Leake [2] in rabbits dying from Vioform. David, Phatak, and Zener [1] believe the toxicity may be dependent more on hyperacidity or intestinal stasis than on the actual amount of the drug administered. Anderson and Reed [3] believe hyperacidity in man can increase the toxicity of Vioform. Anderson, David, and Koch [4] state halogenation of oxyquinoline increased its toxicity in proportion to the atomic weight of the halogen present. David, Phatak, and Zener [1] believe the prolongation of treatment with Diodoquin might increase the danger of absorption and toxicity.

Since direct methods of assay of these drugs are as yet impractical, their absorption after oral administration was studied indirectly by determining blood iodine levels.

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METHOD

The total iodine in whole blood was determined by the method of Matthews, Curtis, and Brodie,[5] based on the method of Leipert,[6] with modifications suggested by Spector and Hamilton.[7] The procedure involved oxidation of the organic matter, and all iodine to iodine pentoxide by means of chromium trioxide in the presence of sulfuric acid. Phosphorous acid was used as a reducing agent for the liberation of iodine during the distillation procedure and a potassium carbonate and sodium sulfite solution to trap the iodine as potassium iodide. Oxidation to potassium iodate with potassium permanganate was accomplished by means of the Groak reaction,[8] and titrations were made using sodium thiosulfate with starch indicator. All determinations were run in duplicate.

TABLE I

Recovery of Iodine Added to Blood

Iodine Content in 10 c.c. Blood	Iodine Added as KI	Total Iodine Recovered	Iodine Recovered
Iodine in Gammas per 100 c.c.			Per cent
21.4	10	30.0	95.5
16.0	10	24.1	92.6
8.0	50	58.6	101.0
11.2	50	59.7	96.0
13.8	100	108.1	95.0
26.2	100	121.9	97.1
13.6	300	301.1	96.0
15.4	300	308.4	98.1
7.2	500	500.1	98.6
12.0	500	508.9	99.4
4.8	1,000	1,000.8	99.6
17.7	1,000	1,002.4	98.5

TABLE II

Blood Iodine Changes Following Treatment with Vioform
Daily dosage: 0.75 gm. (=278 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
M. D. G.	22	215	360	386
E. C.	8	247	—	241
I. R.	13	147	396	374
J. F. S.	48	419	402	349
J. M.	43	412	525	490
J. G.	8	328	314	298
M. T.	11	365	611	529
A. D.	30	244	500	475
Averages	23	297	444	393

Modifications of the original method were as follows:

1. 10 ml. of whole blood were used for each determination and for oxidation 15 ml. of 10 M chromium trioxide and 75 ml. of concentrated sulfuric acid.

2. Destruction of excess chromium trioxide was accomplished by heating the flask in a hood to a temperature of 200 to 210° C. for five to 10 minutes. Gentle rotation of the flask at intervals during heating served to free the walls of any adherent material. It was found unnecessary to run a stream of compressed air through the flask during this procedure as the contents of the combination digestion distillation flask were small in comparison to its liter capacity and foaming soon ceased after a temperature of 200° C. was reached.

3. Several glass beads with holes were preferred to the antibumps recommended in both the digestion and distillation procedures.

4. Before distillation the contents of the flask were diluted with 125 ml. of double distilled water.

5. During distillation 20 ml. of 10 N phosphorus acid were used for the liberation of iodine.

6. In collection of the distillate 1 ml. of a solution 2 M with respect to potassium carbonate and 0.2 M with respect to sodium sulfite was used. [7]

7. In using the Groak reaction [8] to oxidize potassium iodide to potassium iodate, modifications were those suggested by Spector and Hamilton. [7]

Experimental Work and Discussion

Diodoquin and Vioform have been widely used since the above work was published with no deaths reported from their use and no symptoms of toxicity reported other than occasional slight diarrhea, slight gaseous distention, an occasional sense of abdominal warmth, and occasional anal irritation or pruritus ani of a mild degree. Fully 50 per cent of all patients on Vioform and an even larger percentage of patients on Diodoquin register no com-

Table III

Blood Iodine Changes Following Treatment with Chiniofon
Daily dosage: 36.0 grains (=641 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
M. F.	43	69	82	81
R. G.	22	98	69	—
M. J.	10	89	98	84
J. J.	12	37	42	51
I. R.	10	98	106	92
W. S.	3	83	24	21
M. T.	8	118	191	164
Averages	15	85	87	81

plaints. Constipation is sometimes present in Diodoquin, but diarrhea rarely is experienced. Those on Anayodin, Chiniofon or Yatren are more likely to experience diarrhea of moderate degree, but some experience constipation.

TABLE IV

Blood Iodine Changes Following Treatment with Anayodin
Daily dosage: 36.0 grains (=641 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
E. C.	16	81	100	98
J. G.	7	37	125	97
M. H.	11	60	108	108
A. A. K.	22	127	94	97
J. M.	43	212	152	133
J. S.	8	86	48	102
A. V.	23	112	139	—
M. M.	8	35	49	77
Averages	17	94	102	102

Our studies were all made on ambulatory patients who were receiving the drugs for amebiasis and consisted of 33 tests on Anayodin, 27 on Chiniofon, 49 on Diodoquin, and 31 on Vioform. Since all determinations were done in duplicate to minimize error, this represents a total number of 280 blood iodine determinations. It is recognized that an occasional dose was forgotten by the patient, and in two instances where the levels were low in Diodo-

TABLE V

Blood Iodine Changes Following Treatment with Diodoquin
Daily dosage: 28.8 grains (=1,250 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
E. A.	9	772	681	681
H. C.	13	1,702	1,798	1,070
J. H.*	8	114	190	137
E. H.	8	529	510	448
S. H.	11	635	677	620
L. R.	17	444	—	444
J. F. S.	13	482	—	592
V. T.	8	455	455	577
A. V.	15	508		687
C. W.*	12	107	76	24
R. H.	6	994	1,036	956
J. L.	11	752	922	861
A. M.	17	971	918	899
Averages	12	651	692	615

* Note Patients "J. H." and "C. W." mistakenly took 3 tablets per day instead of the prescribed 9.

quin it was found the patient had mistakenly taken only three tablets per day instead of the prescribed nine per day. Diarrhea probably was also a factor in causing lower absorption. Blood iodine determinations were routinely done before the drugs were started, again on the third day, on the seventh day, and at the end of the tenth day. Determinations on Diodoquin were

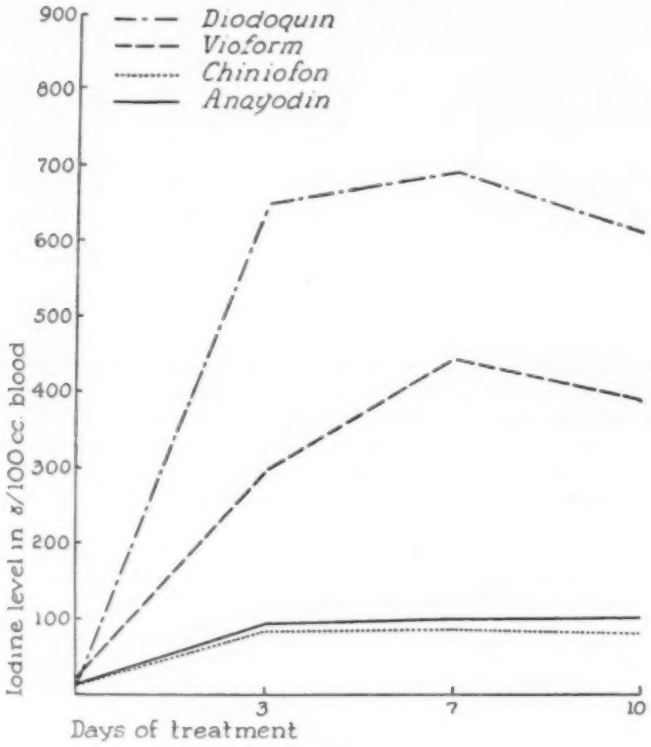

FIG. 1.

also done on the sixteenth and twenty-second days as this drug was routinely given as a course of three weeks but these determinations were not included here since all other drugs are on a 10-day basis. These levels were slightly less than those of the tenth day.

RESULTS

The blood iodine levels before starting the drugs varied between 3 and 43 gammas per 100 c.c. of blood. The average before Diodoquin was 12, before Chiniofon 15, before Anayodin 17, and before Vioform 23. It is

thought the occasional higher values before Anayodin, Chiniofon, and Vioform occurred because Diodoquin was generally given first, and in some cases one of the other drugs was given after a rest period during which the blood levels had not fallen to normal from the previous medication. No initial value before a course of treatment was found to be higher than 17 gammas except when the patient had finished a previous course of treatment within 10 to 15 days.

Anayodin showed a range on the third day of 35 to 212 gammas, the average being 94; on the seventh day of 48 to 152 gammas, the average being 102; and on the tenth day of 77 to 133 gammas, the average being 102. Chiniofon showed a range on the third day of 37 to 118 gammas, the average being 85; on the seventh day of 24 to 191 with an average of 87 gammas; and on the tenth day of 21 to 164, the average being 81 gammas. Vioform showed a range on the third day of 147 to 419, the average being 297 gammas; on the seventh day, 314 to 611 with the average being 444 gammas; and on the tenth day of 241 to 529 with the average being 393 gammas. Diodoquin showed a range on the third day of 107 to 1702, the average being 651 gammas; on the seventh day of 76 to 1798, the average being 692 gammas; and on the tenth day of 24 to 1070, the average being 615 gammas.

The iodine available in the daily therapeutic dose of nine 250 mg. tablets of Anayodin or Chiniofon containing 27.5 per cent of iodine is 641 mg., that of nine Diodoquin tablets of 210 mg. each with 67 per cent of iodine is 1,250 mg., and that of three 0.25 gm. tablets of Vioform containing 37 per cent of iodine is 278 mg. Thus, it appears that the recommended therapeutic dosage of Diodoquin gives the highest value as measured in iodine, Vioform the next highest value, and Anayodin and Chiniofon the lowest iodine value.

When considered in the terms of absorbability as measured by iodine intake and percentage recovery in the blood, Vioform ranks highest, Diodoquin second, and Anayodin or Chiniofon third.

Absorption apparently was uniform for each drug, a fairly high level being reached on the third day, the highest level on the seventh day, then a slight decline on the tenth day which was maintained or lowered in the case of Diodoquin through to the twenty-second day. The explanation is not evident as no quantitative stool or urine determinations were made. The possible interference with absorption through a slightly irritated mucosal lining should be considered in view of the fact that rectal irritation is sometimes noted. A slightly increased number of movements might likewise be a factor in lessening absorption. These drugs not infrequently have a slight diuretic effect, and although no abnormal urinary findings have been reported one might expect increased excretion to occur. Whether the gastric acidity is a factor in absorption has not been determined. The fact that a reasonable blood level of iodine is attained raises a question as to the effectiveness of these drugs on amebae deep in the walls of the intestine or in other parts of the body. It likewise shows none of them are wholly non-absorbable [9] as stated in the Searle publication on Diodoquin in 1937. A gradual

decrease in blood level of iodine after the seventh day should answer the question raised by David, Phatak, and Zener [1] regarding possible increased absorption and toxicity through prolonged administration of these drugs. The drugs are probably effective against the trophozoites in the tissues of the intestines and also against the daughter trophozoites arising in the terminal ileum from the metacystic phase of cystic existence, and in this way probably are of value as a prophylaxis as advocated by Craig [10] against *Endameba histolytica* infection when in ameba infested territory. That they destroy cysts as stated by Manson-Bahr [11] seems open to question, but they can probably prevent cyst formation through destruction of the trophozoites.

Summary

1. Blood iodine studies were conducted on 36 patients who were receiving treatment for amebiasis. Eight patients were given Anayodin with a total of 33 determinations being made. Seven patients received Chiniofon with 27 tests being made. On eight patients receiving Vioform, 31 tests were made. Thirteen patients received Diodoquin as treatment and 49 tests were made. Since these tests were all done in duplicate in order to minimize error, this represents a total of 280 blood iodine determinations.

2. All of the oxyquinoline drugs used in man as amebacides are to some extent absorbed as measured by blood iodine.

3. When considered in terms of milligrams of iodine given, Vioform shows the greatest absorption, Diodoquin second, and Anayodin or Chiniofon the smallest.

4. When given in the recommended therapeutic dosage, Diodoquin gives the highest blood iodine value, Vioform second, and Anayodin or Chiniofon the lowest level.

5. These drugs appear to reach a peak of blood concentration not later than the seventh day and do not appear to be cumulative in absorption or toxicity.

6. If therapeutic value is dependent on iodine absorption, Diodoquin, Vioform, and Anayodin or Chiniofon would rank in the order given in therapeutic effectiveness.

7. Certain factors which may influence absorbability are considered.

8. The question is raised concerning the effectiveness of these drugs in *Endameba histolytica* infection at points other than in the immediate bowel lumen.

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THERAPEUTIC POSSIBILITIES OF PARA-AMINOBENZOIC ACID *

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Para-aminobenzoic acid (PABA) is generally considered to be a member of the B-complex group of vitamins, and is known to be a constituent of many food substances. [1, 2] Although it is a chemical which has long been known, this substance has been of medical interest only during the past decade. From the available literature, however, the principal interest has been largely confined to studies of its effects on bacterial metabolism, pigment metabolism, and other fields of laboratory investigation. The first important clinical use of PABA was evolved during World War II, when it was found to be of value in the treatment of several of the rickettsial diseases. [3] More recently, a series of studies has been directed toward the investigation of further therapeutic possibilities of PABA. Results have been encouraging in a number of diverse conditions of unknown etiology. For example, a beneficial effect has been noted in lymphoblastoma cutis, [4, 5] in certain forms of lupus erythematosus, [6, 7, 8] in active dermatomyositis, [7, 9] in scleroderma, [5, 9] and dermatitis herpetiformis. [7, 10] In addition, it has been observed that PABA will cause a striking fall in the leukocyte counts of patients with chronic myelogenous leukemia. [11, 12] The purpose of this communication is to review briefly the results obtained with PABA therapy in each of these disorders, and thereby direct attention to the apparent broad range of activity of the compound.

For administration to patients, it has been found that para-aminobenzoic acid (PABA) is best tolerated as a neutral salt. This may be in the form of sodium para-aminobenzoate (NaPAB) † or potassium para-aminobenzoate (KPAB).† The latter form (KPAB) is particularly useful in patients who may develop edema on the sodium preparation. KPAB has been used extensively without evidence of potassium intoxication. It should not be administered, however, in the presence of far advanced renal insufficiency. At present, only NaPAB is available in tablet form.‡ For this series of studies, PABA was placed in solution by conversion to KPAB with potassium bicarbonate. The final volume was adjusted to make a 10 per cent solution of KPAB. A 10 per cent solution of NaPAB was prepared in a similar fashion. These preparations have a yellow or amber color and

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† The solutions of NaPAB and KPAB administered to the cases reported herein were prepared from crystalline para-aminobenzoic acid which was generously contributed by Merck and Co., Rahway, New Jersey.

‡ Tablets of "PABA Sodium" were kindly supplied for use in these patients by Wyeth and Co., Philadelphia, Pennsylvania.

darken upon exposure to ultraviolet light. The solutions of PABA salts should, therefore, be kept in a dark place, preferably refrigerated. The compounds are administered orally, in doses of one to four grams (10 c.c. to 40 c.c. if the 10 per cent solution is used), at intervals of two to three hours. Most patients prefer to take the solution with a small amount of milk, fruit juice, ginger-ale, or other soft drink. The size of the dose, the total daily dosage, and the intervals between doses are influenced by the size of the patient, by the clinical entity being treated, and by the clinical status of the individual patient. PABA is rapidly excreted in the urine. This is of importance in treating certain disease entities where it is desired to maintain a high blood level of the compound. The optimal dosage schedules have not yet been determined for the several clinical conditions to be discussed below. That there is considerable latitude in the amount of PABA required, however, will be evident from the respective case histories.

PABA in Leukemia

Study of the effect of large doses of PABA in patients with leukemia was an outgrowth of the work in rickettsial diseases. [3] The mode of action of PABA on the respective intracellular rickettsial organisms is not completely understood. It appears, however, that PABA inhibits rickettsial multiplication by increasing the metabolism of the parasitized cells. [3, 13] This concept of the mechanism of action of PABA in the rickettsioses led to the thought that cells of disordered metabolic function, i.e., neoplastic cells, might not be able to adapt to a substrate containing PABA in high concentration. The latter hypothesis was tested in patients with leukemia. [11] Briefly, it was found that PABA would lower the leukocyte count in chronic myelogenous leukemia. This effect, however, could be maintained only through the continued administration of large amounts of PABA. Furthermore, concomitant clinical improvement was slight and temporary. For these reasons it was concluded that PABA therapy is not to be considered a practical adjunct to the treatment of leukemia. It is to be emphasized that the same opinion is held at this time. The following case report, hitherto unpublished, [14] is given to illustrate the type of response obtained with PABA in chronic myelogenous leukemia. An additional reason for the selection of this particular case will become apparent in the succeeding section.

Case Report

A 43 year old white male was admitted to the University Hospital on May 27, 1947, with the chief complaint of pain in the abdomen. During the preceding year there had been a gradual loss of 20 pounds in weight. Ease of fatigue had been present for six months, and symptoms of hypermetabolism for four months. About two weeks prior to admission, the patient experienced the sudden onset of left upper quadrant pain. This was sharp in character and became more severe on inspiration. The

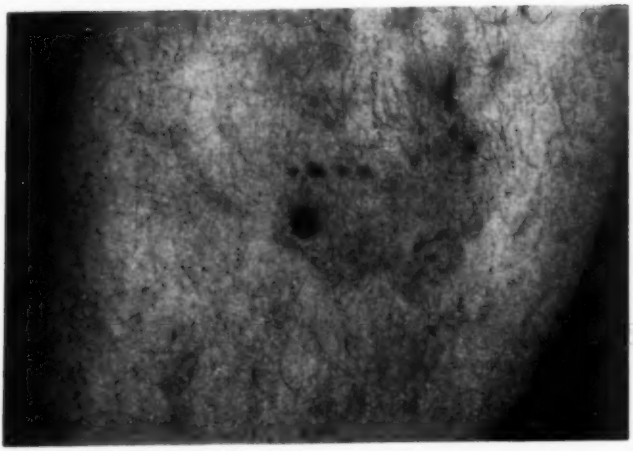

FIG. 1a.

FIG. 1b.

pain radiated to the left shoulder area. He had consulted his physician who referred him to the University Hospital for therapy.

The past history was of no interest except for the occurrence of a skin lesion which appeared on the left thigh in 1927. This lesion was papular and erythematous in nature, and was mildly pruritic. It persisted for several years in spite of treatment and finally disappeared spontaneously. Four years ago a similar lesion appeared on the right calf. This lesion remained essentially unchanged in size and character to the present admission.

FIG. 2a.

Examination of the skin revealed a well demarcated, 6 by 8 cm., raised, erythematous lesion over the medial surface of the right calf (figure 1a). The lesion was superimposed over a mass of varicose veins. Several small lymph nodes were palpable in the axillae and in the inguinal regions. The liver was enlarged to three fingers'-breadth below the right costal margin. It was firm and non-tender. The spleen was very large, extending 20 cm. below the left costal margin in the mid-clavicular line. The remainder of the examination was noncontributory.

Pertinent laboratory findings were as follows: hemoglobin 11 grams per cent; red blood cells 3,500,000; leukocytes 321,000 per cubic millimeter. The white cell differential revealed: 1 per cent basophiles, 2 per cent eosinophiles, 3 per cent lymphocytes, 3 per cent promyelocytes, 32 per cent myelocytes, 17 per cent metamyelocytes and 41 per cent neutrophiles, of which 16 per cent were nonsegmented. The basal metabolic rate was + 64 per cent; plasma cholesterol level 112 mg. per cent. Repeated urine analyses showed a small amount of albumin and 6 to 10 white cells per high power field.

FIG. 2b.

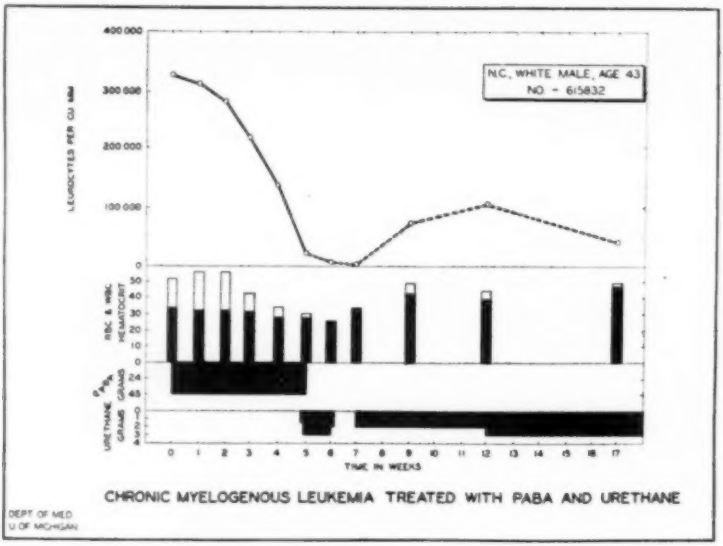
N.C., WHITE MALE, AGE 43
NO. - 615832
LEUKOCYTES PER CU MM
400,000
300,000
200,000
100,000
0
RBC & WBC
HEMATOCRIT
URETHANE GRAMS
TIME IN WEEKS
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
CHRONIC MYELOGENOUS LEUKEMIA TREATED WITH PABA AND URETHANE
DEPT OF MED
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FIG. 3.

After the patient was placed on PABA therapy, a positive test for reducing substances was noted. A biopsy specimen was taken from the skin lesion on the right calf on June 6, 1947. The pathologist reported this to be "premycotic stage of mycosis fungoides; lymphoblastoma cutis" (figure 2a).

While in the hospital the patient was given NaPAB, 4.0 grams every two hours, from June 14, through July 15, 1947. On July 12, the administration of urethane was begun, 3 grams daily. This was discontinued on July 15 because of nausea and vomiting. With this course of therapy, the patient's leukocytes decreased from an initial count of 321,000 to 8,700 per cubic millimeter on July 15. The white cell differential count showed 3 per cent blasts, 9 per cent myeloblasts, 4 per cent metamyelocytes, 19 per cent nonsegmented neutrophiles, and 45 per cent segmented neutrophiles, 1 per cent monocytes, 10 per cent small lymphocytes, 2 per cent large lymphocytes, 2 per cent eosinophiles, and 5 per cent basophiles. The basal metabolic rate had declined to 34 per cent on July 18. The lesion which was present on the right calf had gradually become flat, the erythema faded, and the pruritus ceased (figure 1b). Another biopsy was taken from an area adjacent to the site of the previous specimen. The pathologist noted "the presence of small perivascular infiltrations which would not have been considered diagnostic without previous knowledge of the case" (figure 2b). The patient was discharged with instructions to resume urethane medication a few days thereafter. This was done and the patient's leukemic process has since been well controlled on urethane therapy. In the accompanying chart (figure 3) are given the patient's leukocyte counts and the red blood cell and white blood cell hematocrit values as related to the administration of PABA and urethane.

PABA in Lymphoblastoma Cutis

The patient with chronic myelogenous leukemia described above had a localized infiltrated skin lesion which was diagnosed on biopsy as "premycotic phase of mycosis fungoides." This lesion was observed to regress during the period of PABA therapy. Since lymphoblastoma cutis is considered by many to be a primary lymphoblastoma of the skin, it was deemed justifiable to administer PABA to patients with this disorder. [4] The results of therapy in six subjects have been detailed elsewhere. [4, 5] All experienced relief from pruritus and objective improvement of the skin. This was characterized by diminution in erythema and in the degree of infiltration. Treatment with NaPAB was eventually discontinued in four of the cases because of the development of edema. In two patients, however, edema was circumvented by the administration of KPAB with continued improvement. The case presented below was diagnosed from the history and clinical findings as probable lymphoblastoma cutis. It illustrates the character of change which follows KPAB therapy in patients with this disorder.

Case Report

A 40 year old white male entered the University Hospital on December 13, 1948, complaining of a dermatitis. Ten months previously he had first noted a small, red, scaly, and pruritic area on the lateral aspect of the left ankle. There was a gradual spread of involvement until the entire surface of the body had become red, pruritic, with weeping and crusting. He had consulted a specialist in dermatology who treated

him with superficial roentgen-ray therapy and other measures with definite improvement at first. In late July, 1948, however, the involvement had again become generalized, but the same forms of therapy were then unavailing, and there had been no significant change since.

The past history revealed that the patient had whooping cough at the age of one, following which he was spastic and unable to walk until he was nine years old.

Physical examination revealed an individual with obvious signs of spasticity who appeared chronically ill. There was a generalized erythematous, lichenified, scaling eruption. Small, firm, non-tender, easily movable lymph nodes were palpable in the cervical, axillary, and inguinal regions. The liver was felt two fingers'-breadth below the right costal margin. The edge was firm and non-tender. The remainder of the physical findings were related to the patient's postencephalitic syndrome.

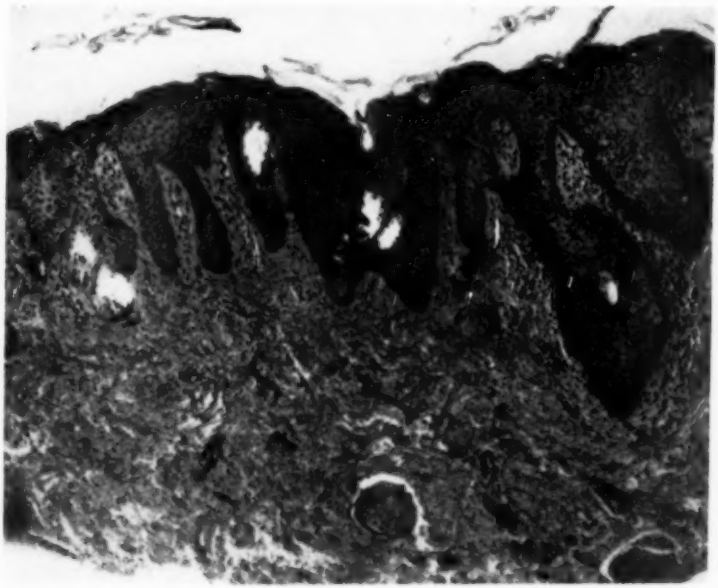

FIG. 4.

Laboratory examination revealed the blood and urine to be normal. After PABA therapy was instituted, however, a reducing substance was detected in the urine. Two biopsies of the skin were taken and two lymph nodes were also removed for histologic study. The skin specimens were reported as psoriasiform eczematoid dermatitis (figure 4). The lymph nodes revealed no definite evidence of lymphoblastoma.

On admission the patient was placed on routine therapy, including starch baths, wet soaks to weeping areas, and calamine liniment. His skin definitely failed to respond to the local measures, however, and pruritus remained a disturbing symptom despite large doses of benadryl. Because of the possibility of a diagnosis of lymphoblastoma cutis, it was decided to undertake a trial of PABA therapy; accordingly, the

patient received 3 grams of potassium para-aminobenzoate every three hours beginning on January 5, 1949. After 10 days, the patient's skin showed definite signs of improvement which was characterized by loss of crusts, cessation of weeping, loss of erythema and infiltration, and diminished pruritus. The patient was discharged from

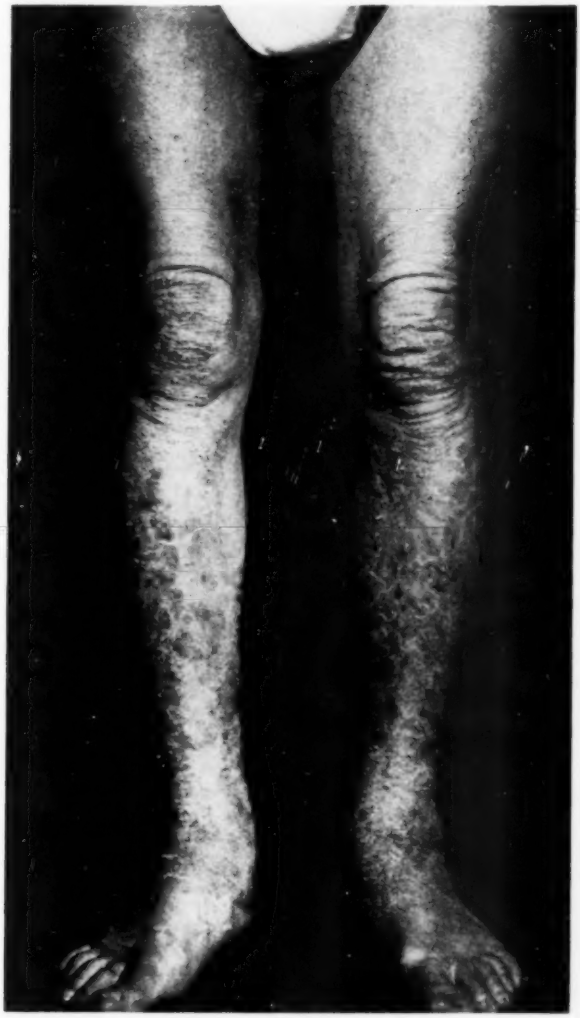

FIG. 5a.

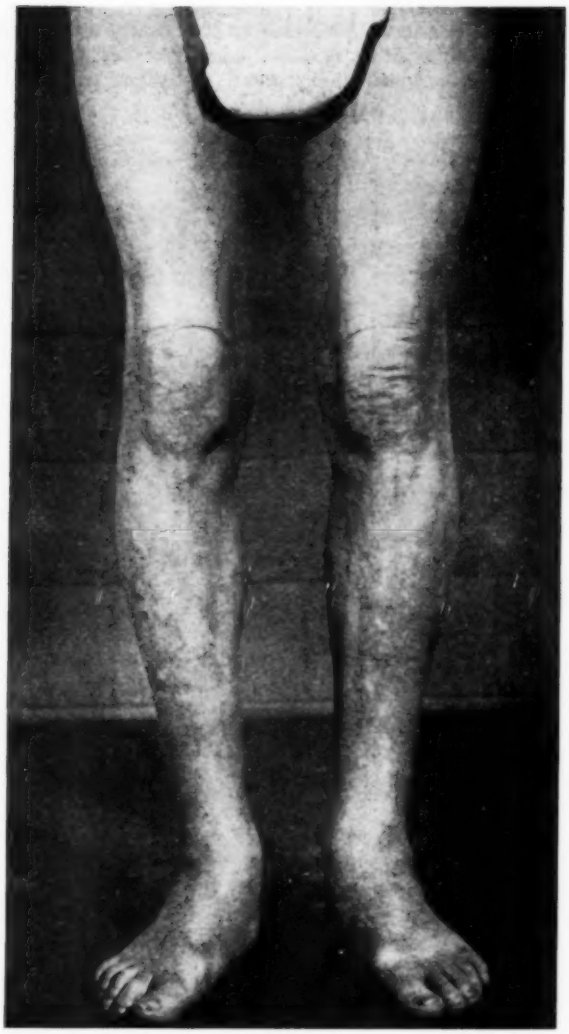

FIG. 5b.

the hospital on January 29, to continue on KPAB, 18 grams daily. The trend of improvement has continued and the program of therapy with KPAB is being maintained at the present writing. The appearance of the patient's legs at the beginning and after eight weeks of therapy is shown in figures 5a and 5b.

PABA in Lupus Erythematosus

Several reports have dealt with the effects of PABA in certain forms of lupus erythematosus.[6, 7, 8] The rationale for administering PABA to patients with lupus erythematosus is based on considerations quite different from those which led to its use in the preceding conditions. There is no general agreement as to the etiology of lupus erythematosus. It is recognized, however, that exposure to sunlight (ultraviolet) may precipitate a relapse or cause an exacerbation of the disease. Sensitivity to sunlight has also been encountered in patients receiving sulfonamide therapy. Since PABA and sulfonamides are metabolically antagonistic, it was reasoned that the former compound might possibly exert a beneficial effect in lupus erythematosus. In view of the experiences in the treatment of the rickettsial diseases [3] and leukemias [11] with large amounts of PABA, it was judged safe to undertake a trial of like therapy in patients with lupus erythematosus. Observations on the effects of PABA in 18 cases of lupus erythematosus have been reported previously. [8] Since that time 15 additional patients have been treated. [15] An attempt to evaluate the results of therapy in the total of 33 patients is given in the accompanying table (table 1). The classification of the clinical forms of lupus erythematosus is arbitrary and is based on criteria indicated by Ormsby and Montgomery. [16] In addition, it is evident that evaluation of the degree of response to therapy can only be an estimate. Generally speaking, when a response was observed, it was characterized by objective improvement in the cutaneous manifestations. Gradual fading of erythema and diminution of the infiltration and edema were usually noted. In some instances a slight exacerbation of the skin lesions has been noted during the first few days of therapy. Regression of these lesions, however, has followed with continued administration of PABA. Many of the cutaneous lesions disappeared completely. Atrophic, scarred, and telangiectatic

Table I

Lupus Erythematosus Treated with PABA, Results in 33 Cases

Type of L.E.*	No. of Cases	Clinical Response			
		None	Poor	Good	Excellent
Discoid	10	2	1	6	1
Chronic Disseminated	10	0	1	7	2
Subacute Disseminated	7	1††	1§	4	1
Acute Disseminated	6	4	1	1	0
Totals	33†	7	4	18	4

* Classified after criteria of Ormsby and Montgomery (1943).
† Totals include 18 cases previously reported in detail.
†† Patient died 4 days after brief course of PABA therapy.
§ Patient died of acute toxic hepatitis on 11th day of treatment; L.E. Lesions clearing at time of death.

areas, however, were not affected. Subjectively, the patients experienced relief of symptoms of pruritus and/or burning in the involved areas. Some noted improvement in their sense of well-being. One patient had marked alleviation of severe arthralgias. In many instances, prolonged administration of PABA is necessary in order to bring about a clinical response. It should also be emphasized that PABA is not curative and that relapses usually occur after cessation of therapy. The first of the case histories described below will illustrate the result attained during eight months of continuous treatment.

Untoward reactions to PABA therapy will be discussed elsewhere in this presentation. It seems pertinent at this point, however, to note that the incidence of reactions to PABA has been greater in patients with lupus erythematosus than in those with other disorders. This may be a reflection of the already well known fact that patients with lupus erythematosus are hyperreactive individuals. Occasionally, patients develop hyperpyrexia while receiving PABA. An example of this type of response is given in the second of the cases presented below. It will be seen from the case summary that "desensitization" can be accomplished when this phenomenon is encountered.

Case Reports

Case 1. A 27 year old white housewife was first seen in the University Hospital outpatient department on July 6, 1948. Approximately one year before the patient had noted the appearance of dusky red papules on the forehead. Shortly thereafter, similar lesions appeared over the entire face and just behind and below the ears. The eruption was more erythematous and became pruritic on exposure to the sun. She had received various forms of therapy for eight months, but the lesions persisted and gradually increased.

On physical examination the abnormal findings were limited to the skin. Scattered over the face were a number of irregularly shaped, discrete, papular, dusky red, scaly lesions which varied in size from 2 mm. to over 1 cm. in diameter (figure 6a).

Laboratory examination revealed a hemoglobin of 12.3 grams per cent and a white count of 8,500 per cubic millimeter, with a normal differential. Urine findings were normal until PABA therapy was begun, at which time a reducing substance was detected. A biopsy specimen was taken from one of the skin lesions and the pathologist observed "slight hyperkeratosis with plugging of dilated hair follicles. Perivascular chronic inflammatory infiltrations are present, and there is slight basophilic degeneration of the collagen in the corium. These findings are compatible with lupus erythematosus, but are not sufficiently advanced to be diagnostic" (figure 7).

The patient was seen in the Dermatology staff conference and the diagnosis of lupus erythematosus was made. Therapy with a mixture of NaPAB and KPAB was begun on July 8, 1948. The patient was instructed to take 18 to 21 grams of medication per day. This program has been continued until the present writing, with the exception of two brief interruptions necessitated by the appearance of nausea and vomiting. During the course of treatment the lesions have shown progressive improvement, as is evident in the accompanying photographs (figure 6b).

Case 2. A 21 year old trained nurse was admitted to the University Hospital on February 5, 1949. She had experienced severe episodes of sunburn during the summer of 1947 and of 1948. In September, 1948, the patient noticed that the skin of each forefinger had become dry and cracked. Within a period of three weeks,

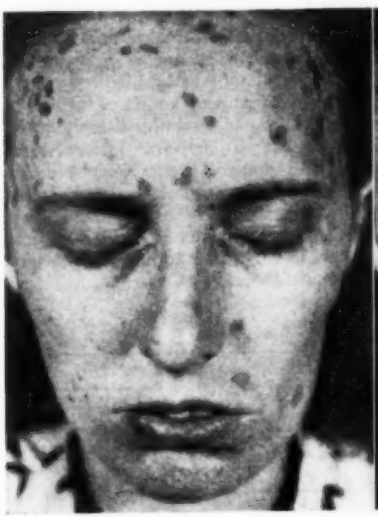

FIG. 6a.

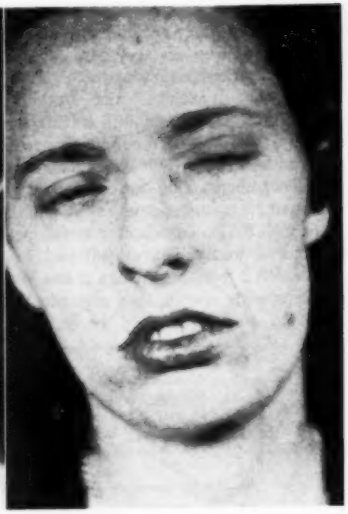

FIG. 6b.

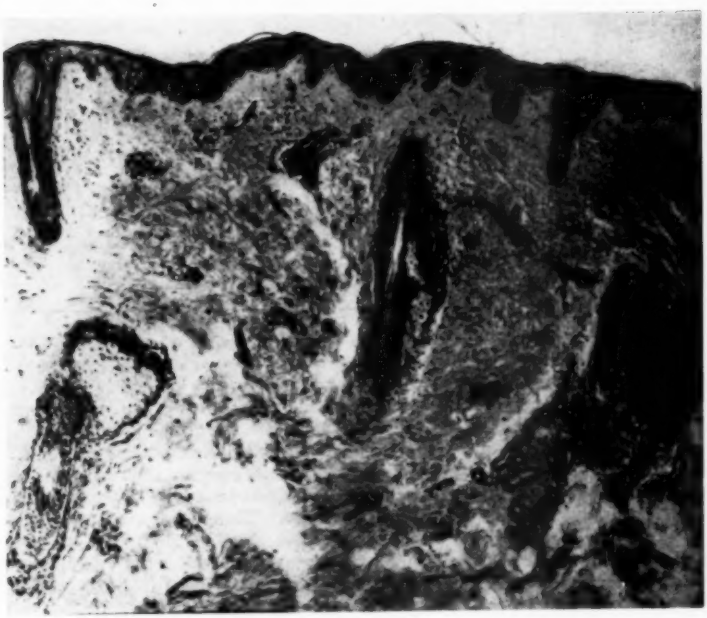

FIG. 7.

pain and swelling appeared in all the fingers. Gradually, the wrists, elbows, shoulders, knees, ankles and toes became similarly involved. She began to have low-grade fever. Periorbital swelling and erythema were also observed. The degree of erythema became more marked on exposure to sunlight. The patient was hospitalized elsewhere three times in November and December, 1948. Treatment consisted of bed rest, aspirin, vitamins, quinine, and intramuscular injections of bismuth. Despite attempts at therapy, however, her condition became worse. Two blood transfusions were administered and the patient was started on NaPAB therapy, 2 grams every three hours, in mid-December. The patient became more severely ill with chills, fever, increased edema, pain, weakness, and rapid pulse. On December 30, the temperature rose to 106° F.; NaPAB was discontinued, penicillin was administered, there was gradual improvement, and the fever fell to its previous level of 100° to 101° F. After two weeks NaPAB was begun again but was discontinued after the second dose because she developed a severe chill and the temperature became elevated to 104° F. Two

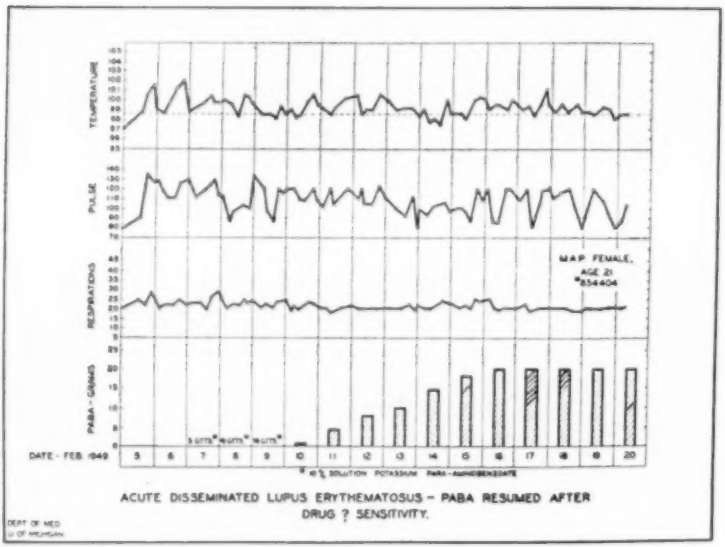

FIG. 8.

days later one dose of 2 grams of NaPAB was administered with similar results. This compound was discontinued entirely and after additional transfusions, the patient was discharged home to remain at bed rest until her admission to this hospital.

Examination revealed a well developed white female in no acute distress. The temperature was 100.8° F.; pulse rate was 136 per minute; respirations were slightly increased. The skin was dry with erythematous areas about the eyes and over each elbow. Periorbital edema was present bilaterally. There were small erythematous nodules over the palmar aspects of her fingers at the interphalangeal joints. A small ulceration was noted on the right border of the tongue. A blowing systolic murmur was heard over the apex. Except for the presence of bilateral inguinal adenopathy, the remainder of the examination was normal.

Laboratory findings revealed normal hemoglobin and red blood cell values (history of recent transfusions). The leukocytes numbered 5,200 per cubic millimeter with a normal differential. Examination of the urine revealed no abnormalities; however, after PABA therapy was instituted, a reducing substance was detected in each specimen. The blood nonprotein nitrogen was 28 milligrams per cent.

The patient's history clearly indicated that the administration of PABA had induced bouts of hyperpyrexia. It was, therefore, decided to begin with minute quantities of the compound in an effort to bring about "desensitization" to PABA. Accordingly, on February 7, 1949, the patient was given 1 drop of a 10 per cent solution of potassium para-aminobenzoate, and this dose was repeated every three hours. As there was no reaction, the quantity was gradually increased and by February 15, the patient was tolerating 25 c.c. (2.5 grams) of the compound every three hours. The patient's fever gradually subsided to near normal levels (see figure 8). Concomitantly, there was subsidence of muscle and joint pains, and the patient was allowed to sit up in a chair for brief intervals. She was discharged on February 20, to continue on KPAB, 21 grams per day. On a return visit two weeks later, the patient's general condition was about the same. Anemia was now evident as she had received no further transfusions. She was, however, tolerating the full amount of PABA which had been prescribed.

PABA in Dermatomyositis

The utilization of PABA in dermatomyositis stems from the foregoing investigations with lupus erythematosus. It will be recalled that the rationale for the use of PABA in the latter condition was based on the factor of ultraviolet light sensitivity. In view of the observed response in patients with lupus erythematosus, it was reasoned that PABA should be given a trial in other disorders which have associated light sensitivity. Hypersensitivity to light is not generally associated with dermatomyositis. One patient with this condition, however, stated that exposure to sunlight aggravated the discomfort in the involved skin areas. Since she was becoming rapidly worse on other attempts at therapy, PABA therapy was undertaken in accordance with the thoughts indicated above. The dramatic result of treatment in this patient has been given elsewhere.[9] The same authors have now treated five patients with features of dermatomyositis, and there has been one death in the group.[17] The remaining four patients have all improved. The first patient to receive PABA for dermatomyositis is still living and active. She has been maintained for 18 months on KPAB. Presented below is the case summary of another patient who is being treated for dermatomyositis.

Case Report

A 38 year old white female had been well until May, 1947, when there appeared edema of the forehead, eyes, and cheeks, associated with erythema of the skin of these areas. This difficulty subsided after a period of two months and she remained in remission until February, 1948. At that time, pain, swelling, redness, and limitation of motion occurred in the knees, ankles, shoulders, elbows, wrists and fingers. This involvement persisted until the time of admission to the University Hospital on September 22, 1948. In addition, she had intermittently a pruritic, tender, erythematous eruption on the palms, soles, and over extensor surfaces of the hands, arms,

and legs. The patient had been continually febrile for at least seven months and had lost 17 pounds in weight. Anorexia, general malaise, and weakness were prominent complaints. She had been seen at the Mayo Clinic in July, 1948, where the diagnosis of dermatomyositis was made.

On examination, the patient appeared to be chronically ill. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic; pulse 110; respirations 20; temperature 101.4° F. A faint erythema and scaling was present on the extensor surfaces of the arms and hands, and on the anterior tibial surfaces. There was limitation of motion of the elbows, wrists, knees, and the interphalangeal joints. The latter were swollen and tender, as were both wrists. The liver was palpable 3 cm. below the right costal margin, while the spleen could be felt 2 cm. below the left costal margin. Neither organ was tender. The remainder of the physical examination was negative.

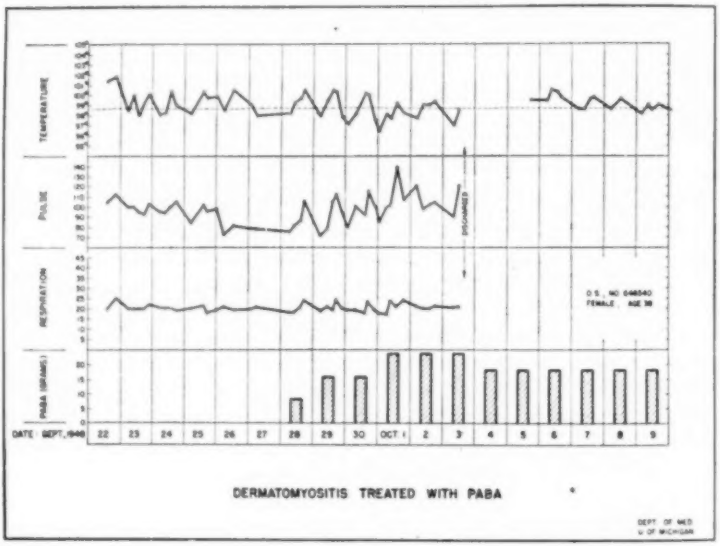

FIG. 9.

Admission blood and urine findings were not remarkable except for a hemoglobin of 12 grams per cent. The 24 hour urinary creatine excretion was found to be 760 milligrams on September 23. An ultraviolet skin sensitivity test showed the patient to be three times as sensitive as normal. Muscle and skin biopsies were taken from the left pectoral area. Microscopic examination revealed slight perivascular monocytic infiltrations in the dermis. More marked perivascular monocytic infiltration was present in the subcutaneous adipose tissue and in voluntary muscle. The pathologist interpreted these findings as being compatible with the diagnosis of angiomyositis.

After the preliminary studies were concluded the patient was placed on PABA therapy, 2 grams every three hours initially. There was a gradual fall in temperature towards normal (figure 9) and the patient felt subjectively improved. She was discharged on October 3 to continue on 18 grams daily of KPAB, and to return for monthly check-ups. By mistake the patient took two times the prescribed amount of drug and had a severe gastrointestinal upset. After a few days, however, therapy

was resumed at 12 grams daily. The patient has continued on this program to the present time. She has been afebrile since mid-October, 1948. Appetite, strength and sense of well-being have gradually returned. The joint involvement subsided markedly but there has been residual stiffness, which, however, is also improving.

PABA in Scleroderma

Lupus erythematosus, dermatomyositis, and scleroderma are often grouped together as "diffuse collagen disorders." [18] It was natural, therefore, that the studies of the effects of PABA in the former conditions should lead to a desire to test its value in patients with scleroderma. An added stimulus arose during the course of PABA therapy of a patient who had features of both dermatomyositis and scleroderma. Since the patient showed remarkable improvement in both aspects of his condition, the transition to therapy in scleroderma was enhanced. The results of treatment in this patient and four additional cases of scleroderma have been described.[9] Improvement occurred in all, and was greater when the involvement was extensive. The sclerodermatous areas gradually softened and became thinner and more pliable. There was a consequent increase in range of motion of affected parts. In some patients there has been observed a definite decrease of pigment in previously hyperpigmented areas. The administration of PABA salts has been extended to additional cases of scleroderma.[17] Summaries of the records of two of these patients are given below. The first patient represents more or less the classical picture, whereas the second case emphasizes the fact that visceral involvement is a common accompaniment of scleroderma. An interesting therapeutic problem arises in connection with the intestinal involvement exemplified by the second patient. It is likely that there is softening of the wall of the intestinal tract during KPAB therapy just as softening of the skin occurs. Conceivably, this might precipitate marked intestinal dilatation with signs of ileus. For this reason, it is believed that all patients with scleroderma should have a complete roentgenologic examination of the gastrointestinal tract prior to the institution of treatment with PABA. In the event widespread small bowel involvement is encountered as in the case below, treatment should be cautiously undertaken. In the light of present knowledge, it seems best to begin with small doses (e.g., 4 to 6 grams per day). Subsequently, the dosage schedule may be augmented as the patient's progress warrants.

Case Reports

Case 1. A 40 year old white housewife was admitted to the University Hospital on September 9, 1948. One year before she had noted the onset of numbness and tingling in the fingers. Later the fingers became swollen and it was necessary to have her wedding band cut off. In the six months preceding admission to the hospital, there had been a gradual increase in pigmentation of the skin, especially over exposed parts. In addition, there had been progressive weakness and a weight loss of 40 pounds despite a fair appetite. More recently she had noticed a sensation of

tightness and swelling in the lower legs. The patient also complained of episodes of substernal burning which had occurred since March, 1947. These attacks of discomfort usually appeared at night while lying in bed. There were no other signs or symptoms referable to the gastrointestinal tract.

On physical examination the patient appeared chronically ill. There was a diffuse hyperpigmentation over the face, anterior sternal area, the forearms and hands. The skin over the forehead was somewhat atrophic and bound down, as was the skin over the clavicles and over the dorsal aspects of the hands. There was swelling of the proximal interphalangeal joints with limitation of motion. Dependent cyanosis of the finger tips was noted. The skin of the lower extremities showed similar changes to those noted in the hands. The liver was palpable 5 cm. below the right costal margin in the midclavicular line. The remainder of the examination was negative.

Laboratory findings included the following: hemoglobin 12.0 grams per cent; leukocytes 13,400 with a normal differential; repeated urine analyses were negative except for the appearance of a reducing substance when the patient received PABA therapy. The urine creatine excretion was 0.48 gram for the 24 hours of September 8. An ultraviolet skin sensitivity test revealed the patient to have two times the

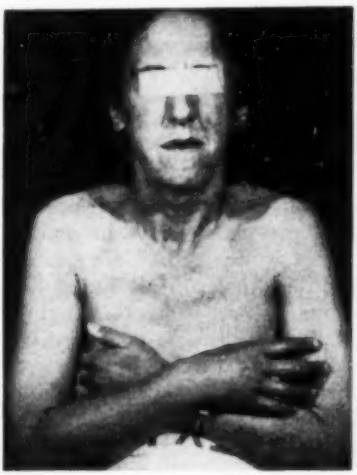

FIG. 10a.

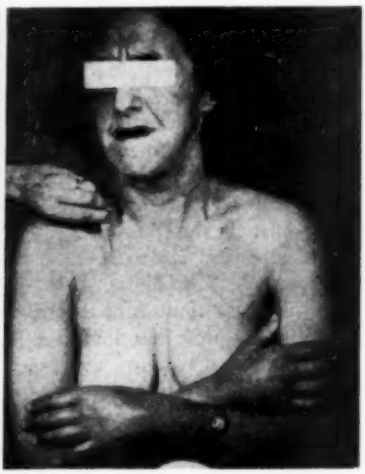

FIG. 10b.

normal sensitivity. A punch biopsy specimen was taken from the skin of the hand and was histologically compatible with a diagnosis of scleroderma. Roentgen examination of the hands revealed cystic osteoporosis, more marked in the left carpal bones, with destruction of the distal ends of the terminal phalanges of the three middle digits of the right hand. A roentgen-ray examination of the upper gastrointestinal tract was negative.

While in the hospital the patient was started on a 50–50 mixture of NaPAB and KPAB, 2 grams every three hours. Therapy was well tolerated and the patient was discharged on September 23 to continue with six doses a day of 3 grams each. When next seen on October 1, there had been very evident softening of the involved skin areas. Treatment was continued until October 7, at which time the patient developed

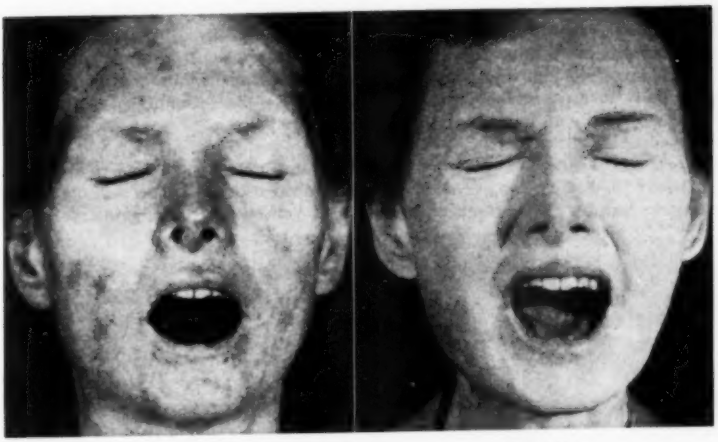

FIG. 11a.

FIG. 11b.

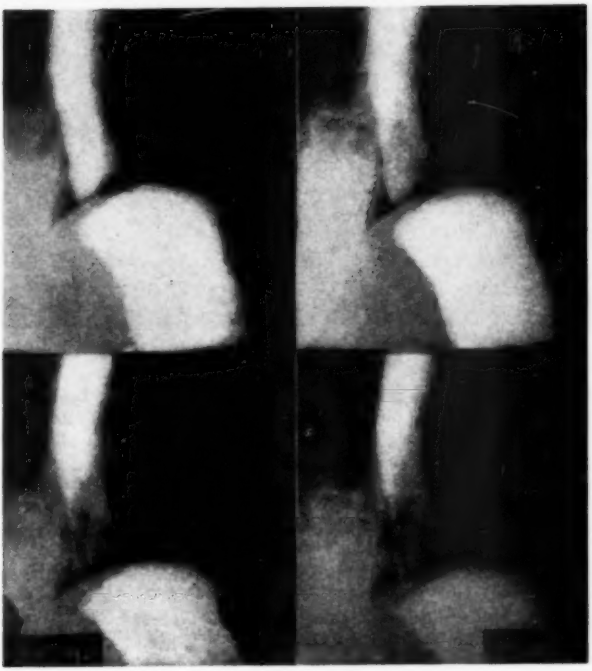

FIG. 12.

nausea, vomiting and fever. PABA was discontinued until December 3 when it was resumed at five drops each three hours. As there was no reaction, the dose was progressively increased on succeeding days. By December 10, the patient was taking 6 grams daily. The amount was gradually increased and the patient has averaged 12 grams daily to the present writing. In addition to the softening of the skin, there has been depigmentation (figures 10a and 10b). The patient is also experiencing less retrosternal discomfort.

Case 2. A 50 year old white housewife was admitted to the University Hospital on August 19, 1948. For five or six years she had had considerable discomfort from epigastric burning with frequent nausea and vomiting. Since January, 1948, the

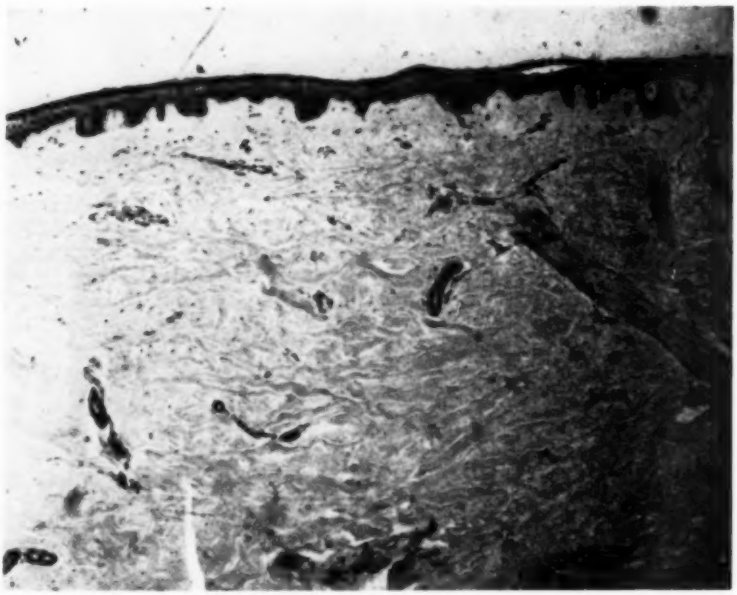

FIG. 13.

patient had experienced greater distress with cramping pains, distention, and constipation. The vomitus was observed to contain food ingested the previous day. There had been a gradual weight loss of 20 pounds. Tightness of the skin of the face, fingers, and hands had been present for several years and was progressing slowly. A rash had appeared on the face a few months prior to admission to the hospital.

Examination revealed an erythematous, scaling, crusted eruption on the skin of the forehead, face and behind the ears. The skin was thickened on the face, neck, arms, hands and shoulder-girdle. There was limitation of motion of the fingers, and the mouth could not be opened widely (figure 11a). The abdomen was greatly distended and tympanitic. A succussion splash was present. The remainder of the physical examination was within normal limits.

Laboratory examination revealed the urine and stool to be normal. The hemoglobin was 12.7 grams per cent. The leukocytes numbered 2,400 per cubic millimeter

with the following differential count: 41 per cent neutrophiles, 2 per cent eosinophiles, 29 per cent large lymphocytes, 20 per cent small lymphocytes, and 8 per cent monocytes. The 24 hour urinary creatine excretion was 660 milligrams. An ultraviolet skin sensitivity test revealed the patient to have three times the normal sensitivity. Roentgen examination of the gastrointestinal tract revealed a normal colon. There was a cuff-like narrowing of the distal esophagus (figure 12) and profound neuromuscular abnormality of the small bowel. A skin biopsy specimen was taken from the dorsal aspect of the right forearm and revealed homogenization of fibrous connective tissue in the dermis (figure 13).

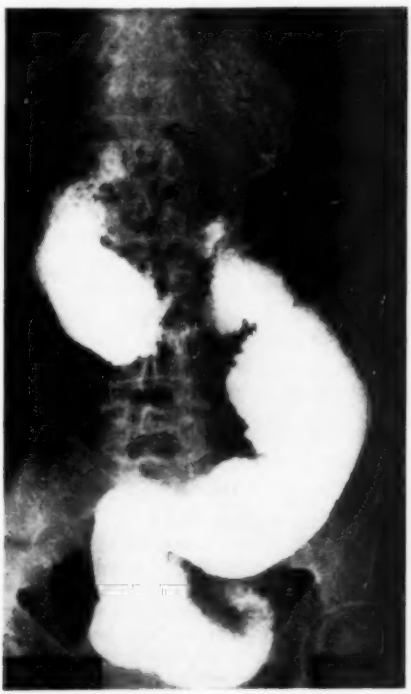

FIG. 14.

Initial treatment was directed toward relief of the partial intestinal obstruction. Wangensteen suction was instituted and decompression accomplished. There was gradual relief of symptoms, and PABA therapy was begun on September 2. From 18 to 24 grams daily were administered during the first weeks of treatment.

On this regimen, the patient's skin softened slowly and became loose at the previously hide-bound areas. The patient was able to open her mouth more widely (figure 11b), and the eruption on the face cleared. Episodes of abdominal distention and constipation continued but were less frequent, and nausea and vomiting no longer occurred. Another gastrointestinal roentgen-ray examination was performed on November 24. It revealed loss of gastric and esophageal peristaltic activity

and profound disorder of small bowel function. This was evidenced by the extremely dilated loops of jejunum and duodenum with greatly delayed passage of barium. The opaque medium was still in mid-jejunum at five hours (figure 14). In view of these findings, it was decided to continue with PABA therapy but at a reduced dosage of 6 to 9 grams daily. The patient has tolerated this medication with continued improvement in gastrointestinal function and of the cutaneous manifestations. Concomitantly, there has been a definite gain in strength with ability to resume her household activities.

PABA in Dermatitis Herpetiformis

Para-aminobenzoic acid administered in large amounts has also been shown to suppress the manifestations of dermatitis herpetiformis. [7, 10] This disorder is usually well controlled with sulfapyridine or Asiatic pills. [16] Occasionally, however, forms highly resistant to the usual treatments are encountered. The first patient to receive a trial of PABA therapy for dermatitis herpetiformis was severely afflicted and had not responded to other medications. [10] The reason for trying PABA in that particular patient was the fact that exposure to sunlight caused more intense pruritus of the lesions. In the five cases reported elsewhere, improvement was observed in all.[10] Usually there was complete disappearance of bullae and other skin lesions. In some instances, a few scattered lesions remained. Pruritus gradually subsided and then disappeared. It is of interest that the process recrudesced about 8 to 10 days after cessation of PABA therapy. Upon resumption of treatment, control of the lesions is reëstablished. In the patients so far observed, continued suppression requires continued administration of PABA. The following case report illustrates the effect of PABA in dermatitis herpetiformis.

Case Report

A 78 year old white female was admitted to the University Hospital on July 9, 1948. Eight weeks previously, her eyelids and lips had become swollen. On the following day, a pruritic red rash appeared in the left antecubital space. She had taken no unusual medications at the time of onset. Within two or three weeks, the erythematous eruption had spread to involve both arms, the abdomen, lower back, thighs, and legs. Bullae appeared on the arms. Pruritus was intense.

On examination the pertinent findings were limited to the skin. Infiltrated, erythematous, plaque-like lesions were present on the lower arms, chest, abdomen, lower back, buttocks, and thighs. Several large bullae were present in the left antecubital space. The largest of these was 2.5 cm. long and 1.5 cm. wide, and contained a clear, straw-colored fluid. All of the bullae were tense. There were no mucous membrane lesions.

Laboratory examinations revealed the urine to be normal. Blood values were within normal limits except for a slightly elevated white count of 11,360 per cubic millimeter. The differential count revealed 6 per cent eosinophiles but was otherwise not remarkable.

The patient was treated with wet dressings, calamine liniment, and daily liquor carbonis detergens baths. The diagnosis of dermatitis herpetiformis was made and sulfapyridine, 0.5 gram, four times daily was started on July 12. This was discontinued on July 15 because of nausea. On July 20, administration of potassium para-

aminobenzoate, 1 gram every three hours, was begun. This was gradually increased over the next three days to 3 grams at three hour intervals for five doses. The patient also received superficial roentgen-ray therapy. On this regimen, the lesions gradually regressed and there was only residual hyperpigmentation at the time of discharge on August 15. The KPAB dosage schedule had been reduced to 6 grams daily on August 10. Within 10 days lesions began to reappear. The amount of KPAB was increased to 18 grams daily and the lesions again subsided. Activity of the process in this patient appears to be suppressed by 15 to 18 grams daily of the compound. This program of therapy is being continued at the present writing.

Discussion

The clinical course of an individual patient who has one of the foregoing disorders may be unpredictable. It is believed, however, that sufficient patients in each group have been treated with para-aminobenzoic acid to allow a preliminary evaluation. It appears quite evident from the data available that the causal relationship between therapy and response has been too consistent to be attributed to chance remission. That the improvement observed in these patients is due to the administration of PABA is further supported by the fact that relapse usually occurs after cessation of therapy.

The response observed in patients with chronic myelogenous leukemia does not justify the use of PABA in patients with leukemia. In regard to the remaining entities, however, it is believed that PABA may be of value in selected cases. It will be recalled that in these patients all of the usual forms of therapy had been tried and abandoned before PABA therapy was instituted. The most gratifying results have so far been attained in lymphoblastoma cutis, scleroderma, and certain cases of dermatomyositis. Results of therapy in acute disseminated lupus erythematosus have been disappointing as may be noted in the accompanying table. On the other hand, there has been sufficient benefit noted in two cases of the acute form to warrant trial of PABA in additional patients. Dermatitis herpetiformis is usually controllable with other forms of medication. In instances of intolerance to the usual treatment, however, para-aminobenzoic acid therapy may be used.

The mode of action of PABA in these diverse conditions is not known. All of the disorders are of unknown etiology and the pathogenesis of each is poorly understood. It is, therefore, unprofitable to speculate at this time as to the possible mechanisms involved. Surely the diseases referred to above cannot be considered to result from PABA deficiency, since the dosages employed are far greater than the trace amounts required for physiologic vitamin-enzyme activity. [19]

A number of toxic manifestations have been encountered during PABA therapy. The most serious of these was a fatal case of toxic hepatitis.[8] In addition, drug fever and dermatitis medicamentosa have been observed. When drug fever appears, it is possible to "desensitize" the patient as was illustrated in one of the case reports above. It has already been noted that an initial exacerbation of the skin manifestations of lupus erythematosus is

sometimes seen. It also appears worthy of interest that the preponderance of reactions to PABA have occurred in the lupus erythematosus group of patients.

Nausea, at times associated with vomiting, is the most frequent reaction. This usually subsides after omission of a few doses of the drug. Therapy has often been resumed in such cases without further difficulty.

Leukopenia may be present in patients who are receiving PABA. It is difficult to decide whether this is due to the compound, since several of the above named conditions are characterized at certain stages by a low white blood cell count. There have been no cases of agranulocytosis from PABA. In the light of experiences with other substances, however, it is possible that this might occur rarely in patients receiving PABA. This possibility should be kept in mind.

A reducing substance has been detected in the urine of all patients taking large amounts of PABA. This was believed to be glucose as a result of findings with osazone and other tests. [11] Additional studies have given evidence that this may not be glucose. [20] This finding raises certain implications not hitherto recognized. It is especially important in that at least two instances of hypoglycemic attacks have been observed during the administration of PABA. [17] Through investigations now in progress it is hoped to explain these observations.

From the studies referred to herein, it is concluded that para-aminobenzoic acid has therapeutic possibilities in several diseases of unknown etiology. These are lymphoblastoma cutis, certain forms of lupus erythematosus, dermatomyositis, scleroderma, and dermatitis herpetiformis. Apart from the immediate practical considerations, it is hoped that additional study of the effects of para-aminobenzoic acid will yield information as to the mechanisms involved in these obscure disorders.

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GONOCOCCAL ARTHRITIS: A STUDY OF 202 PATIENTS TREATED WITH PENICILLIN, SULFONAMIDES OR FEVER THERAPY *

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Washington, D. C.

Prior to March, 1932, only symptomatic measures were available for the treatment of gonococcal arthritis. At that time, it was observed during a course of fever therapy for syphilis that the gonococcal arthritis also present had improved.[1] Further studies confirmed this original observation and fever became the accepted form of therapy. Several years later the sulfonamides were introduced and most recently penicillin became available. Since these three methods of treatment have received extensive trial at the Gallinger Municipal Hospital, it appeared worthwhile to review these cases. They have been analyzed in the present paper, with particular reference to the efficacy of these three methods of treatment.

Selection of Cases

The charts of all patients discharged with the diagnoses of gonococcal arthritis from January 1936 through November 1947 were reviewed. Criteria for including a patient in this study were similar to those suggested previously by Spink and Keefer.[2] In the presence of inflammatory rheumatism the diagnosis was considered definite if organisms morphologically resembling gonococci were found on smear or culture of the joint fluid. This was particularly true if the organisms were also found by smear or culture of exudate from the genitourinary tract. The diagnosis was considered probable in the absence of positive bacteriologic findings in the joint fluid, provided the organisms were found in specimens taken from the genitourinary tract and other studies did not indicate another type of arthritis. Similarly a positive complement-fixation test was accepted as probably diagnostic in the absence of positive bacteriologic findings in the joint fluid or the genitourinary tract, when other forms of arthritis were ruled out.

It is our opinion that the complement-fixation test is reliable for the establishment of the diagnosis of gonococcal arthritis since about 80 per cent [3-6] of patients with gonococcal arthritis have a positive complement-

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fixation test in the blood or joint fluid. In chronic gonorrhea the test is positive in only 35 per cent and almost invariably negative during the acute stage of gonorrhea. Muether and Andrews [7] stated that they rarely found false positives while false negatives do occur occasionally. In our series, the complement-fixation test was done on the joint fluid or blood in 99 patients and was found to be positive in 81 (82 per cent). In 30 instances, there was other confirmatory evidence of a gonococcal infection.

Even though there was a history suggestive of recent gonococcal infection, the case was not included in our series unless the above criteria were fulfilled. Patients were included in the series, however, even in the absence of a history of gonorrhea. We believe that the inability to elicit a history of gonorrhea is of little value in excluding gonococcal arthritis because of the long interval which may intervene between the genitourinary infection and the arthritis [8, 9] and the difficulty of establishing the diagnosis in females.

Age, Sex and Joint Involvement

Included in our series are 109 (53.9 per cent) males and 93 (46.1 per cent) females. Others [3] have stated that the incidence of gonococcal arthritis in males is four to five times that in females.

Eighty-five per cent of the cases occurred between the ages of 20 and 40 in the males, and between the ages of 10 and 30 in the females.

Table 1

Joints Involved in 202 Cases of Gonococcal Arthritis

Joint	Monarticular 39 Patients	Polyarticular 163 Patients
Knee	23	162
Ankle	3	126
Wrist	9	69
Shoulder	1	56
Hip	1	56
Elbow	1	51
Feet and toes	0	38
Hands and fingers	0	26
Thoracic and lumbar spine	1	8
Cervical spine	0	7
Sternoclavicular	0	7
Temporomandibular	0	3

Gonococcal arthritis is usually a polyarticular disease [3, 5, 10–12] although it is frequently stated that it is monarticular in involvement. A possible explanation for this belief is the fact that after a period of migratory arthritis, in which most of the joints are only slightly affected, the involvement persists in one of the joints, particularly one involved early in the disease. In our series, monarticular involvement occurred in only 39 patients, while 163 had polyarthritis. In table 1 the incidence of involvement of the various joints is tabulated.

Results of Treatment

The duration of the infection prior to the time of treatment was determined for each patient and correlated with the response to therapy. On this basis it was found that the patients could be grouped into those whose symptoms were less than 30 days' duration, and those treated after the thirtieth day. For purposes of classification the former were designated as "acute" and the latter as "chronic."

The response to treatment was evaluated solely on the basis of freedom from evidence of infection rather than upon the functional result. There are many patients who are cured of the infection but remain crippled as a result of the disease.

Symptomatic Treatment. Eleven patients who were admitted during the period of study received only symptomatic treatment. Nine recovered and two were discharged against advice, on the second and eleventh hospital days, respectively, without improvement. Although some patients with gonococcal arthritis recover spontaneously, these results are obviously not indicative of the efficacy of this method of therapy. These patients happened to improve while they were undergoing diagnostic studies before specific therapy was instituted. By contrast, there were numerous patients being studied who did not improve until specific therapy was instituted.

Fever Therapy. A course of fever therapy was given to 55 patients. Fever was induced by two methods, radiant energy (Kettering hypertherm), and typhoid vaccine intravenously. The results of these two methods were so different that they will be discussed separately.

An adequate course of therapy in the Kettering hypertherm consists of at least four sessions at three to five day intervals during which time a temperature of 106° F. to 106.5° F. is maintained for six hours.[10, 13, 14] In our patients treated by this method, therapy appeared to be adequate in 33 patients, 21 (63.6 per cent) of whom recovered. When the cases were divided into "acute" and "chronic" varieties, it will be seen from table 2 that 77 per cent of the patients treated during the "acute" stage recovered, whereas, only 55 per cent of those in the "chronic" stage responded favorably.

It is obvious that the prognosis was much more favorable in those treated promptly. This difference in the response of the "acute" and "chronic" cases to hyperthermia has been noted by many investigators.[3, 10, 11, 13-15] There appeared to be no difference between the results in the "chronic" patients who became "chronic" while receiving other treatment unsuccessfully and in those who procrastinated in presenting themselves for therapy.

Previous attacks of arthritis did not influence the outcome of treatment with the hypertherm cabinet. Ten of the 16 patients who had previous arthritis recovered, compared with 11 out of 17 with no previous attacks.

Of the 22 patients given typhoid vaccine intravenously 10 (45.4 per cent) had a favorable response. These patients were in the "acute" stage. Eight with "acute" and four with "chronic" infections failed to respond. These

data are shown in table 2. Although these results appear disappointing, they probably do not represent an accurate picture of what can be expected from this form of therapy. An accepted technic consists of sessions during which a temperature of 105° F. to 106° F. is maintained for two to five hours [16] plus the proper use of diet, sedation and accessory heat in the form of blankets and hot-water bottles. If the injection of 50 to 100 million organisms does not produce a temperature of 102° F. within two hours, another injection of 50 to 100 million organisms should be given. This may be repeated again in an hour or two if necessary in order to achieve the proper febrile response. After careful review of the plan of therapy in each of our cases in no instance could the technic be classified as adequate.

TABLE II

Results of Therapy in Gonococcal Arthritis

Type of Therapy	Acute Arthritis						Chronic Arthritis						All Cases	
	With Previous Arthritis		Without Previous Arthritis		Total		With Previous Arthritis		Without Previous Arthritis		Total			
	R*	F†	R	F	R	F	R	F	R	F	R	F	R	F
Fever Cabinet	4	1	6	2	10 (77%)	3	6	5	5	4	11 (55%)	9	21 (63.6%)	12
Fever Typhoid vaccine	4	4	6	4	10 (55.5%)	8	0	3	0	1	0 (0.0%)	4	10 (45.4%)	12
Sulfonamides	16	12	66	15	82 (75.2%)	27	3	13	12	3	15 (48%)	16	97 (69.3%)	43
Penicillin	0	3	21	5	21 (72.4%)	8	0	1	2	0	2 (66.7%)	1	23 (71.8%)	9

* Recovered from all evidences of the infection.
† Failed to recover from the infection during the period of treatment.

Sulfonamide Therapy. Of the 140 patients treated with sulfonamides 97 patients (69.3 per cent) recovered (table 2). In order to determine the effectiveness of the sulfonamides several factors had to be considered: (1) the duration of the infection, (2) a history of previous attacks of arthritis, (3) the particular sulfonamide employed, (4) the total dose administered, and (5) the duration of therapy.

Sulfanilamide was employed in 63 patients, sulfapyridine in 19, sulfathiazole in 36, sulfadiazine in 15, and sulfamerazine in 7. These results are tabulated in table 3 and since the results with each sulfonamide are essentially the same, the sulfonamides will be considered as a whole.

Early treatment played a significant part in the response to therapy. Recovery occurred in 82 (75.2 per cent) of those patients who were treated within 30 days of the onset of the arthritic symptoms, whereas 15 (48 per

cent) recovered who were treated after the lapse of the 30 day period (table 2). The occurrence of previous arthritic attacks appears to be an even more significant factor. The results in the group of patients who gave no history of previous attacks of arthritis are similar whether treated "early" or "late." On the other hand, in those patients with a previous arthritic history there is a pronounced difference in the response to sulfonamides. A favorable response occurred in 16 (57 per cent) out of 28 patients in the "acute" group, whereas only three (19 per cent) out of 16 recovered in the "chronic" group. These differences are statistically significant.

TABLE III

Results of Sulfonamide Therapy in Gonococcal Arthritis, Arranged According to the Individual Drugs Used and the Year of Treatment

	1938		1939		1940		1941		1942		1943 to 1946		Total	
	R*	F†	R	F	R	F	R	F	R	F	R	F	R	F
Sulfanilamide	17	2	10	4	18	9	1	1	1	0			47 (75%)	16
Sulfapyridine			1	0	4	5	3	2	2	2			10 (53%)	9
Sulfathiazole					2	2	16	2	6	4	2	2	26 (72%)	10
Sulfadiazine							0	2	5	1	4	3	9 (60%)	6
Sulfamerazine											5	2	5 (72%)	2
Total	17 90%	2	11 73%	4	24 60%	16	20 74%	7	14 67%	7	11 61%	7		

* Recovered from all evidences of the infection.
† Failed to recover from the infection during the period of treatment.

It has been suggested that in acute gonorrhea the sulfonamides are becoming progressively less effective as a result of inadequate therapy and the consequent development of resistant strains of gonococci. Thus it was deemed necessary to calculate the total amounts of sulfonamides utilized by the patients in this series. Whereas, during the year 1938 the average total dose ranged from 30 to 39 grams, the average doses employed in 1940 varied from 60 to 69 grams. The explanation for the maintenance of the recovery rate in the later years may have been the increased dose of sulfonamides. The increase in total dosage not only represents an increase in the amount but also in the duration of therapy. In table 4 it can be seen that in the later years therapy was continued for a longer period of time. Figure 1 graphically presents the results of sulfonamide therapy in relation to the duration of

TABLE IV

Results of Sulfonamide Therapy in Gonococcal Arthritis Arranged According to the Duration of Therapy

Days	1938		1939		1940		1941		1942		1943 to 1946		Total		Per Cent Recovered
	R*	F**	R	F	R	F	R	F	R	F	R	F	R	F	
0–3	1	1	1	0	0	3	0	2	0	0	0	0	2	6	25.0
4–6	4	0	3	1	6	5	1	2	1	1	1	1	16	10	61.5
7–9	5	1	3	2	5	1	5	2	5	1	3	1	26	8	76.4
10–12	1	0	1	0	5	3	5	0	2	3	4	1	18	7	72.0
13–15	2	0	2	0	1	1	2	0	2	0	1	1	10	2	83.3
16–18	1	0	1	0	2	0	1	1	3	2	0	1	8	4	66.7
19–21	1	0	0	0	0	1	3	0	1	0	2	1	7	2	77.7
21	2	0	0	1	5	2	3	0	0	0	0	1	10	4	71.4

* Recovered from all evidences of the infection.
** Failed to recover from the infection during the period of treatment.

therapy. The best results were obtained in patients treated for nine days or more.

Penicillin Therapy. We have treated 32 patients with penicillin since the introduction of this antibiotic, 23 (71.8 per cent) recovered. Fourteen of these cases have previously been reported.[17] These results are not an accurate representation of the value of penicillin, however, since among the nine failures three patients were treated with a total dose of 300,000 units

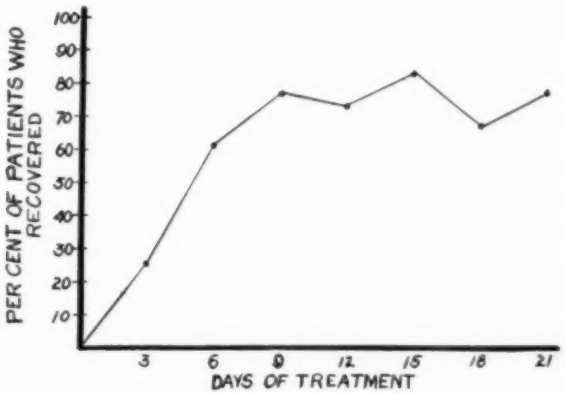

FIG. 1. Results of sulfonamide therapy in relation to the duration of therapy.

or less over a period of 30 hours or less, and another received 225,000 units daily for four days intramuscularly, plus 350,000 units intraarticularly. An additional patient who failed to recover received 225,000 units of penicillin intramuscularly for two days and 2,400,000 units of penicillin orally for the same period of time. The four other failures occurred in patients who received 2,200,000 to 21,600,000 units of penicillin for 10 to 21 days.

Of the 27 patients who received a total dose of 1,000,000 units or more, intramuscularly, 21 recovered, and of the 26 patients treated for more than five days 22 (84 per cent) responded favorably (table 5).

TABLE V

Results of Penicillin Therapy in Gonococcal Arthritis Arranged According to the Total Dose Administered and the Duration of Therapy

Total Dose of Intramuscular Penicillin (units)	Recovered	Failed to Recover
0–1 Million	2	3
1–2 Million	4	1
2–5 Million	9	2*
5 Million and over	8	3
Total	23 (71.8%)	9
Duration (days)		
0–1	0	2
1–2	0	1
2–4	1	2
4–5		
5–10	10	1
10 and over	12	3
Total	23 (71.8%)	9

* Includes one case treated with 550,000 units intramuscularly and 2,400,000 units orally.

Prognosis was independent of the duration of symptoms before the institution of therapy. Twenty-nine patients were classified as "acute" cases and three as "chronic." Twenty-one of the former, and two of the latter recovered (table 2).

As with the previous form of therapy, the results in the 28 patients who had no previous history of arthritis were better than in the four who had previous arthritic histories. The difference is statistically significant. Twenty-three (82.1 per cent) of the former and none (0.0 per cent) of the latter recovered.

Our experience with intraarticular penicillin is limited to two patients in whom it was given in addition to parenteral therapy, one of whom received a single injection and the other two injections. One recovered and the other failed to improve. From a review of the literature it would appear that unless the destructive process is as pronounced as in other pyogenic types the use of penicillin locally is of no added value.

Combined Therapy. In 23 instances the sulfonamides were combined with fever therapy. Among these, combined therapy was employed origi-

nally in 14 patients, and in the case of the others it was given after other methods had failed. As noted previously, when used alone the cabinet method of inducing hyperthermia showed a decided superiority over typhoid vaccine injection. There were no failures in 14 patients treated with the combination of sulfonamides and the Kettering hypertherm. Approximately 50 per cent of those treated with sulfonamides and typhoid vaccine failed to improve. It appears that there is no advantage to giving combined therapy initially, since the results are not significantly better than when this method is used after other forms of therapy had failed, and the rigors of such therapy are considerable.

Two patients were treated from the start with a combination of fever and penicillin. One patient with a chronic infection recovered after receiving three typhoid vaccine injections, plus 440,000 units of penicillin over a period of three days. The other patient had an acute infection and was undoubtedly treated inadequately, receiving 240,000 units of penicillin in four divided doses at four hour intervals plus three fever cabinet treatments over a period of five days. A combination of sulfadiazine and penicillin resulted in cure in one acute case.

Discussion

Three different methods of therapy are available and have received a fairly extensive trial in the treatment of gonococcal arthritis. It is important to review the results with each form of therapy so that the best method of treatment can be utilized. Prior to the development of specific therapy, the use of the available symptomatic measures was occasionally rewarded with success. In 1929, Key [18] stated that gonococcal arthritis is often self-limited, while, on the other hand, the affected joint seemed to be doomed regardless of any treatment employed. He further stated that joints which contain considerable excess fluid and are only moderately tender and in which there is relatively little periarticular thickening, clear spontaneously regardless of treatment.

Stecher and Solomon [14] were convinced that a satisfactory result was attained without medical intervention in a significant proportion of patients. Recovery followed bed rest and joint protection. Myers and his associates [19] reported that 25 per cent of a series of 33 patients recovered spontaneously.

On the other hand, in an analysis of 200 cases, Culp reported poor results in 34 patients whose treatment was limited to bed rest and sedation. Forty-nine patients who were given baking, diathermy, massage, prostatic massage, and passive motion failed to recover. An additional 41 patients who were treated by aspiration and the injection of air, hot compresses, manipulation under anesthesia, immobilization, incision and drainage, failed to respond.

The introduction of hypertherm treatment was a major step forward. The results with the use of the Kettering hypertherm are generally good, yielding recovery rates which ranged from 53 per cent to 90 per cent.[3, 9-11, 13-15, 20, 21] Most reports indicate about 75 per cent of patients recover.

Keefer [9] stressed that results were less striking in the chronic cases. Our findings are essentially in agreement.

On the other hand, few reports of the results of the typhoid vaccine method of therapy are variable. Culp [3] stated that he obtained poor results, whereas Spink and Keefer,[2] reported 18 recoveries out of 24 patients. It is not possible to determine the relative value of this type of treatment from a review of these reports.

Other methods of fever therapy (such as the intramuscular injection of the Corbus-Ferry filtrate, malaria inoculation and the intravenous injection of milk) have been used with varying success.[5, 10, 11] The disadvantages of these procedures are that they are inconstant in fever-producing properties and frequently provoke serious, uncontrollable, and occasionally fatal reactions.

The sulfonamides have a definite bacteriostatic effect upon gonococci Spink and Keefer [22] showed that sulfanilamide was capable of sterilizing the synovial fluid within a short time after ingestion. Later Keefer and Rantz [23] pointed out that sulfanilamide diffused into the synovial fluid in about the same concentration as that of the blood, and that when the sulfanilamide concentration of the synovial fluid was maintained above five milligrams per cent the fluid was sterilized with regularity. Hench [24] stated that sulfanilamide was as promptly successful as fever therapy. Later other sulfonamides were shown to be as valuable.[3, 9, 25–29]

When the sulfonamides alone fail to cause improvement, a significant number of patients can be salvaged by combining these drugs with fever therapy. Similar results have been reported by others.[13, 25] Some investigators are of the opinion that the use of combined therapy has shortened the hospital stay, has produced marked and rapid relief from pain, and has restored function more rapidly.[7] However, the rigors of fever therapy must be considered.

Although our results show relatively good response to sulfonamides, the trend toward a decrease in efficacy of these drugs against the gonococcus appears definite [30] and must be seriously considered in the choice of therapy today.

Penicillin has been very successful in the treatment of gonorrhea and at present may be considered the drug of choice in the treatment of gonococcal arthritis. When adequate doses are given for a sufficient period of time, a recovery rate at least equal that produced by other methods may be expected. Moreover, since the drug is easily administered and toxic reactions, especially those of a serious nature, are so rare, it is preferable to the other methods of therapy discussed.

The duration of therapy appears to be as important as the total dose, for almost all the patients in our group who were treated for less than five days did not respond. On the other hand, 22 (84 per cent) of 26 patients recovered when treated for longer than five days.

The use of intraarticular penicillin usually is not necessary though its use has been suggested in those cases in which there has been no definite improvement with systemic penicillin alone.[30] A previous study by one of us showed that penicillin diffused rapidly into the joint fluid when given systemically.[31] Secondly, since gonococcal arthritis is not a disease of the synovial cavity, but of the synovial and periarticular tissues, the concentration of penicillin in the synovial cavity is relatively unimportant, as compared with the concentration in the tissue fluid. The four patients who gave a history of previous episodes of arthritis did not respond. The explanation may be similar to the one proposed for such diseases as mastoiditis, osteomyelitis, or endocarditis; namely, that the amount and density of the scar tissue, which has a poor blood supply, permits only partial and probably inadequate penetration of the penicillin. In these cases, still greater amounts of penicillin may effect a higher percentage of favorable responses. If penicillin in large doses is not effective, fever therapy may then be used.

Summary and Conclusions

1. Two hundred and two patients with gonococcal arthritis have been treated by various methods. Treatment with the Kettering hypertherm resulted in recovery in 21 (63.6 per cent) of 33 patients. Better results were obtained in patients treated during the acute stage. Typhoid vaccine was used intravenously in 22 patients. The results are not conclusive because in no case could the therapy be considered adequate.

2. Sulfonamides were used in 140 patients with favorable results in 97 (69.3 per cent) of patients. The duration of the disease did not have so great an effect upon the outcome as did the existence of previous episodes of arthritis. Only 43.1 per cent of the patients with previous attacks responded favorably, whereas 81.2 per cent without previous episodes did well. Moreover, there appeared to be a definite tendency toward a progressive decrease in the efficacy of the sulfonamides during the past few years.

3. Penicillin was given to 32 patients of whom 23 (72 per cent) recovered. Of those who were adequately treated, recovery occurred in 84 per cent. As with sulfonamides the previous episodes of arthritis had a greater bearing on the outcome than did the duration of the present symptoms.

4. Penicillin is the drug of choice in the treatment of gonococcal arthritis. It is recommended that two to five million units of penicillin administered over a period of five to ten days be used. Since sulfonamides are the simplest to administer, they may be tried first if desired, and should always be employed in those patients who do not respond to penicillin. Fever therapy is probably the most efficacious form of therapy in those patients who have a history of previous attacks of arthritis, but because of the dangers involved in such therapy it should be the last resort after penicillin and sulfonamides have failed to bring about recovery.

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OBSERVATIONS ON PRIMARY COCCIDIOIDOMYCOSIS *

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During the war years coccidioidomycosis ("Valley Fever," "Desert Fever") has received rather intensive study as the result of the concentration of armed forces personnel in the endemic areas of California and the Southwest. The present paper concerns itself with observations on 43 cases of primary coccidioidomycosis seen at the Station Hospital, Williams Air Field, Chandler, Arizona during 1946 and 1947.

Since 1935 when Dickson and Gifford [1, 2] pointed out that infection with *Coccidioides immitis* may have a mild or primary form as well as the disseminated form originally described by Posadas [3] in 1892, a wealth of information has accumulated on the subject. It does not serve the purposes of this paper, however, to attempt a review of these writings or to give more than a brief background of the etiology and pathogenesis of the disease.

The causative agent of coccidioidomycosis is the fungus *Coccidioides immitis*. The fungus exists in two stages: The saprophytic stage ends in the formation of the chlamydospore which is the infective stage for man. The parasitic stage which is seen only in animal tissues, sputum, or exudate is recognized as a doubly refractile spherule containing endospores. The infective chlamydospore is most often inspired with dust, although rarely it may enter the body through the skin. The fungus has a particular affinity for the respiratory tract, however, and only a negligible number of infections have their origin elsewhere.

Emmons [4] feels that the disease is primarily a disease of rodents, which is transmitted to man only through accidental contact with dust previously contaminated with spores from infested rodents.

Smith [5] has classified infections with *C. immitis* in the following useful and distinct manner:

1. Initial or primary infection (self limited, nearly always respiratory).
   a. Asymptomatic form (commonest form which involves most residents of the endemic sections).
   b. Acute respiratory, influenzal, or pneumonic form.
   c. Either of the above types associated with erythema nodosum or erythema multiforme.
   d. Pulmonary cavity form (probably a complication of b).

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2. Progressive disseminated form (coccidioidal granuloma). Our discussion will be concerned entirely with the initial or primary infection described above.

Material, Procedure, and Methods

We have studied 43 cases of considered proved coccidioidomycosis. The patients' ages varied from 18 to 35 years. There were 39 males and four females. Of the 39 males, there were seven Negroes and one Filipino. There were no deaths in the series.

Although it has been stated that recent entry into an endemic area, positive coccidioidin skin test, and elevated sedimentation rate are sufficient to make the diagnosis,[6] we have included only those cases which could definitely be established as coccidioidal by laboratory confirmation. In most cases we have used the complement fixation and precipitin serological tests as performed through the courtesy of Dr. Charles E. Smith, Stanford University, to establish the diagnosis. In two cases, demonstration of the fungus in the sputum has been confirmatory.

In each case we have noted the length of time in the endemic area, relative degree of exposure to dust, symptoms, physical findings, results of skin testing with coccidioidin, sedimentation rate, chest roentgenograms, serological tests, length of hospitalization, and follow-up progress.

The coccidioidin for skin testing was supplied by Dr. C. E. Smith. Unless otherwise noted, this was used in a dilution of 1:1000, prepared from undiluted material once a month.

Five of the patients were transferred to Army General Hospitals for further observation and care because of the fear of dissemination. The remainder were all followed at the Station Hospital, Williams Field, Arizona.

Results

Length in Endemic Area. The shortest time any individual had been in the area was one month; the longest was 19 months. The average of all cases was six and one-half months.

Dust Exposure. This was rated on the basis of 1 to 4 +. No particular exposure was rated as 1 +, moderate chronic exposure such as working on outside details as 2 +, severe chronic exposure (working in motor pool or airplane flight line) as 3 +, and a heavy exposure definitely recalled by the patient as having occurred within three weeks of the onset of illness as 4 +.

Fifteen were rated as 1 +; seven were rated 2 +; six were rated 3 +; and nine as 4 +. The remainder were not rated.

Symptoms. 1. Chest pain was by far the most common symptom. Thirty-nine of the patients (90 per cent) complained of pain, characteristically aggravated by respiration or coughing. In most cases the pain was substernal and poorly localized. It was most often described as "right in the middle," or "under the breastbone."

It is noteworthy that this pain which may be severe at the time of admission almost always subsides within one or two days of hospitalization. It was the unusual case which persisted in having pain longer than 48 hours.

2. Cough was a complaint in 19 of the cases (44 per cent). This was most often nonproductive in nature and disappeared within several days of hospitalization.

3. Malaise was a prominent symptom in 14 cases (32 per cent). Although it was mentioned specifically by only 32 per cent, nearly every patient on questioning was willing to admit fatigue and general sense of ill being. In most cases this symptom was found to persist for a longer period of time than any other symptom.

4. Fever and chills were symptoms in 13 cases (30 per cent). The fever in most cases was low grade and, similar to the chest pain and cough, disappeared within the first two or three days of hospitalization. The highest temperature at time of admission was 103°.

5. Headache, usually generalized, was complained of by 12 patients (28 per cent).

6. Substernal pain on swallowing was a feature in 11 of our patients (25 per cent). Although it was noted by only one in four, we have observed that when present it is one of the most characteristic symptoms of primary coccidioidomycosis, and its existence is extremely suggestive of the disease.

The discomfort is usually beneath the upper sternum, and at times may be of sufficient severity that the patient will refuse solid food and limit himself to liquids.

7. Mild sore throat was a feature in six cases (14 per cent).

8. There were two patients who were admitted with hemoptysis. In both cases the sputum was only blood streaked and was small in amount.

9. Two patients complained of right upper abdominal pain and are further described under physical findings.

Skin Manifestations. A total of 14 per cent of the patients exhibited allergic skin lesions. Four patients (9 per cent) had erythema nodosum, limited to the pretibial surface of both legs. Two patients (5 per cent) had erythema multiforme distributed over thighs, buttocks, and sacral region.

Physical Findings. The physical findings were so inconstant, and when present were of such questionable accuracy as to make statistical figures of no value. It is interesting to note that two patients were admitted with severe right upper abdominal pain and sufficient muscle guarding to justify the admitting diagnosis of gall-bladder colic. Both of these were discovered to have pulmonary infiltration above the right diaphragm.

Coccidioidin Skin Testing. The skin test was carried out on all patients. 0.1 c.c. of 1 : 1000 Coccidioidin was injected intracutaneously in the forearm and read at 48 hours. The reaction was read as 1 to 4 +, using the following criteria of Cheney and Denenholz [7]:

1 + Induration and erythema 0.5 to 1 cm.
2 + Induration and erythema 1 to 2 cm.
3 + Induration and erythema greater than 2 cm.
4 + Vesiculation in addition to erythema and induration.

Fifteen were read 1 +, 16 as 2 +, nine as 3 +, and two as 4 +. One patient was initially negative in the 1 : 1000 dilution but was found to be strongly positive with the 1 : 100 dilution.

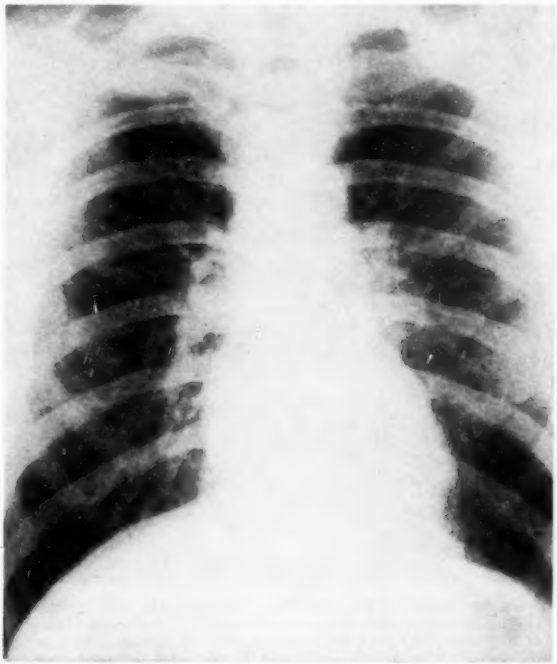

FIG. 1. Lobular infiltration and thickened hilar markings on the left in an 18 year old white male who had been in Arizona for one month. Hospitalized following four days of substernal pain and malaise. Coccidioidin skin test 3 plus and sedimentation rate 21 mm. per hour. Total hospitalization 25 days. Film five months later revealed persistent nodular remnant of previous infiltration, although patient was asymptomatic and sedimentation rate normal. Serological confirmation was obtained.

Sedimentation Rate. Sedimentation rates (Wintrobe tube method) were done on admission and repeated at weekly intervals until normal. Elevation above the normal was found in every case. The highest initial rate in our series was 51 mm. per hour (uncorrected). The average rate on admission was 32 mm. per hour (uncorrected).

Chest Roentgenograms. All but one of our cases presented abnormal findings on roentgen examination of the chest. The types of involvement seen included (1) diffuse pneumonia-like infiltrations, (2) hilar thickening, (3) hilar and mediastinal adenopathy, (4) nodular parenchymal lesions, (5) cavitation, and (6) effusion. None of our cases exhibited bony involvement of the chest cage. In evaluating and classifying this series of films we were aided by previous reports on the roentgen findings of coccidioidomycosis.[6, 8, 9]

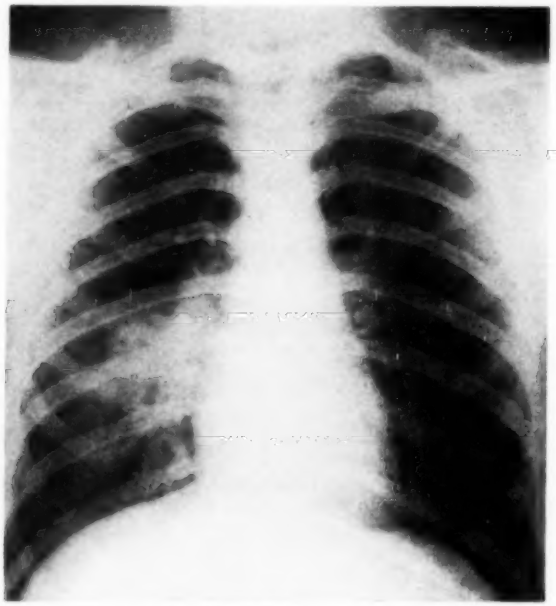

FIG. 2. Bronchopneumonic-like infiltration and moderate hilar thickening on the right in an 18 year old white male who had been in Arizona for one year. Hospitalized after five days of malaise and substernal pain, and two days of erythematous rash on arms and trunk (erythema multiforme). Coccidioidin skin test 2 plus, and sedimentation rate 27 mm. per hour. Serological confirmation was obtained. Hospitalized for 12 days.

1. Pneumonia-Like Infiltrations. These were by far the most common radiologic findings, being present in 35 cases (83 per cent). The majority of these (21 cases) were isolated, peripheral, lobular infiltrations which were well circumscribed and of homogeneous density (figure 1). Ten of these infiltrations involved the lower lobes, and 10 the basal portions of upper lobes. In one case the involvement was apical and closely resembled active reinfection tuberculosis. Abnormally thickened hilar shadows are a frequent accompaniment of this type of infiltration, and less frequently true hilar adenopathy has been noted. Complete resolution of the peripheral infiltrations

occurred within five days to three months (average 20 days) in 11 of these cases. Resolution in the others was incomplete in from one to 10 months, and characteristically left a discrete fibrous nodule at the site of the infiltration. Cavitation subsequently occurred in two of these nodules.

The other 14 cases of pneumonia-like infiltration were fan-shaped in type and radiated from the hilar region outward into a lung field (figure 2). They most resembled primary atypical pneumonitis. Eight of these infiltrations involved lower lobes (one bilaterally), three involved the basal portion of an upper lobe, and three were situated in the apex of an upper lobe.

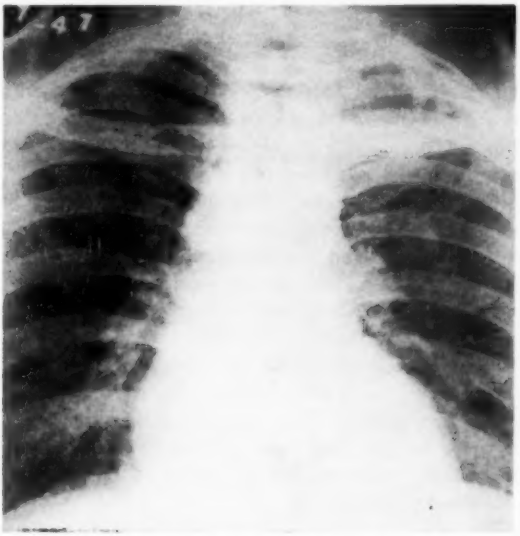

FIG. 3. Marked mediastinal widening, slight left hilar thickening and adenopathy, and fan-shaped left apical infiltration in a 27 year old negro male who had been in Arizona for three months. Two week history of cough and dull pain in left upper chest. Coccidioidin skin test 3 plus, and sedimentation rate 50 mm. Serological confirmation obtained. Sedimentation rate still elevated after one month.

All three of the apical cases simulated active reinfection tuberculosis. Coexistent thickened hilar markings were frequent, and somewhat less frequently hilar and mediastinal adenopathy, and basal effusion was present. Complete resolution occurred in five days to three months (average one month) in seven cases, and in the remaining seven cases incomplete resolution in one to 10 months. This last group included four of the patients who were transferred to General Hospitals because of the fear of dissemination.

2. Hilar Thickening. This was noted in 28 cases (66 per cent), and consisted of soft peribronchial infiltration which produced fuzzy, widened

bronchovascular markings, often difficult to evaluate. In six of our cases this constituted the only roentgen finding, although the remaining 22 had associated peripheral infiltration, as mentioned above. Slow resolution (three weeks to seven months) was a feature of those which showed only thickening.

3. Hilar and Mediastinal Adenopathy. These findings were noted in 19 cases (45 per cent) (figure 3). Twelve showed hilar adenopathy alone, and seven exhibited both hilar and mediastinal adenopathy. The association of adenopathy with parenchymal infiltration has been mentioned previously. Resolution occurred in periods which varied from seven days to nine months, and was noted to be much more rapid when the mediastinal glands were not involved. Those with both hilar and mediastinal adenopathy resolved very slowly.

4. Nodular Parenchymal Lesions. Although discrete fibrous nodules have been said to represent the most characteristic and diagnostically specific finding in primary coccidioidomycosis, we noted that when present they represented incomplete resolution of a previous coccidioidal infiltration, usually of the lobular type. Serial films showed nodule development from a previous infiltration in six cases over periods of time which averaged 5 months. The nodules averaged 2 cm. in diameter, were single, isolated, well circumscribed, and showed no evidence of calcification. They were equally distributed between the upper and lower lobes.

5. Cavitation. Two of the nodules mentioned above progressed to cavitation, the first undergoing transformation from a lobular infiltration to a discrete nodule to cavity in 11 days. The other cavitation occurred slowly over a period of eight months. These cavities remained practically static for periods of five to 10 months, and were further characterized by lack of inflammatory change in the surrounding area, a moderately thin wall, and upper lobe involvement (figure 4).

6. Pleural Effusion. This was noted in three cases and was associated in all three with parenchymal infiltrations. Effusion was minimal in the right costophrenic sulcus and along the right lesser fissure in two cases, but was massive in the third and obscured the entire left lower lobe (figure 5). The minimal effusions cleared within three days, while the massive effusion cleared in 21 days.

Serological Tests. Through the courtesy of Dr. Charles Smith, Stanford University, complement fixation and precipitin determinations were made on nearly all of our cases. We have used this service almost entirely to confirm the diagnosis, rather than to follow the progress of the disease. It would have been desirable to have repeated studies on each case especially as a check on the possibility of dissemination, but due to the time and distance involved we have limited ourselves to one determination, usually performed between three or four weeks after the onset of symptoms.

Treatment. Treatment in every case consisted of bed rest until chest films and sedimentation rates were improved, and sharply limited activity in the hospital until the sedimentation rate was normal and chest films were either clear or static for at least one week. Symptomatic therapy such as salicylates and cough mixtures were used as necessary. Chemotherapy was not attempted.

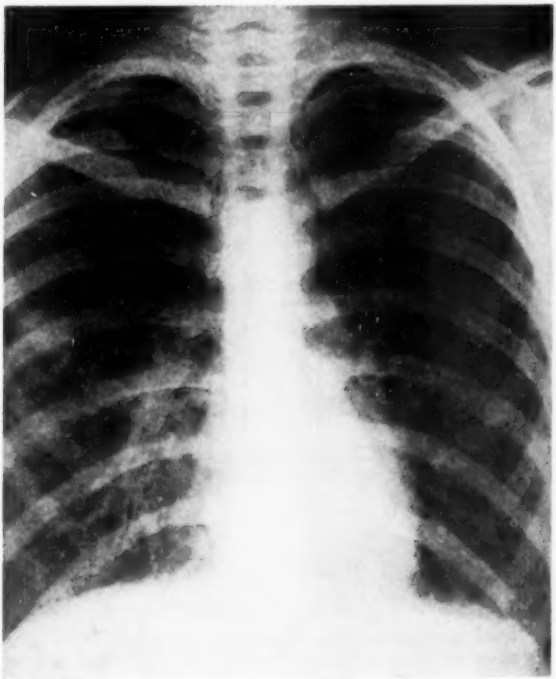

FIG. 4. Discrete cavity in the right mid-lung field with moderate right hilar thickening in a 15 year old white female who had been in Arizona for one year. Initial lesion was lobular infiltration in the same area one month previously. Coccidioidin skin test 3 plus, sedimentation rate 37 mm. per hour. One month later this lesion regressed to a nodule, and five months later appeared unchanged. Serological confirmation was obtained.

Length of Hospitalization. The average length of hospitalization at this station was 21 days. The longest hospital stay was 42 days, and the shortest was 10 days. For the six patients transferred to a General Hospital, the average length of hospitalization was 120 days, although none of the cases was found to exhibit the disseminated stage. The hospital stay of the negro patients averaged six days more than the white patients.

Follow-Up of Cases. We have been able to follow 22 of our cases by personal interview for periods varying from two months to one year. All but two patients stated that they had no symptoms and felt "as good as ever" at the time of interview. However, nearly all admitted having fatigue for the first few days following discharge from the hospital.

Both of the patients who claimed sequelae described vague chest pains on exertion and stated that they still felt tired and weak after five months. Radiologic studies of the chest and sedimentation rates were repeated and found normal.

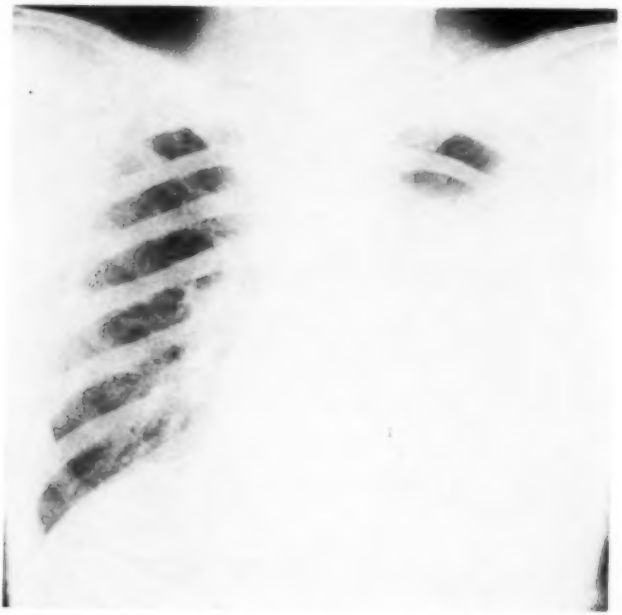

FIG. 5. Massive left pleural effusion and moderate right hilar adenopathy in a 26 year old Filipino male who had been in Arizona for four months. Hospitalized following two days of severe left chest pain and cough. Coccidioidin skin test 2 plus and sedimentation rate 23 mm. per hour. *Coccidioides immitis* demonstrated in sputum, and serological confirmation obtained. Effusion completely cleared in less than one month.

Incidence of Positive Kahn Tests. Routine Kahn tests were performed on each patient using the Standard Kahn accepted by the U. S. Army.

Three of these were returned as positive. The first was in a 19 year old negro male who denied any history of syphilitic infection, malaria, or yaws. The test was repeated and again returned as positive. Since it is our policy to check our own positives with quantitative Kahns and Wassermanns performed in the 6th Army Laboratory, San Francisco, a sample of serum was

forwarded for confirmation. Unfortunately this was apparently lost in transit. Another Kahn was performed in our laboratory two weeks later and reported as doubtful. Five weeks after the initial positive reports, another specimen was found negative and continued negative on two subsequent examinations at monthly intervals.

The second case was a 28 year old white male who similarly denied history of infection. The initial Kahn performed in our laboratory was positive. This was confirmed by a 6th Army report of 20 Kahn units although the Wassermann was negative. After five weeks, the Kahn became doubtful, and at six weeks turned negative. This was confirmed by another negative specimen taken one month later.

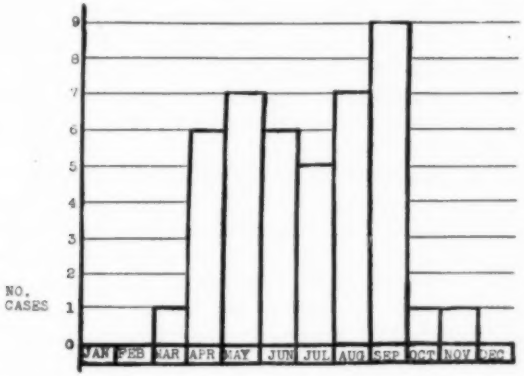

CHART 1. Incidence of coccidioidomycosis according to months.

The third case was a 20 year old Negro male who had been treated for latent syphilis at the induction station 15 months previously, using combined penicillin and heavy metal therapy. He had been followed in our Venereal Disease Clinic at monthly intervals and had had four negative Kahns during that time. Following hospitalization for coccidioidal infection, the Kahn was reported positive and continued positive for two months, at which time he was transferred to another station.

Seasonal Incidence. (See chart 1.)

DISCUSSION

One general fact which has impressed us in observing coccidioidomycosis over two seasons has been the relative well being and comfort of the patient once he has been in the hospital for one or two days. Despite markedly elevated sedimentation rates, extensive pulmonary infiltration, and even fever, the patient will state that he feels well and would like to be up and about. Our greatest problem has been to make the patient appreciate the

necessity of bed rest in the absence of symptoms. For this reason each patient is told at the time of admission something of the nature of his illness, the reason for adequate rest, and the approximate length of time he will be hospitalized.

We have also confirmed the fact that the Negro, in general, exhibits more severe symptoms than the white, is more susceptible to the disease, and has a longer convalescent period.

Dysphagia, or pain on swallowing, as mentioned previously, has been of value to us many times in differentiating coccidioidomycosis from the more common simple respiratory infections. We feel that this is best explained by an extensive hilar adenitis or low grade mediastinitis, and perhaps an esophagitis, but we have been unable to make any particular investigation to substantiate this belief. Undoubtedly we have placed more reliance on dysphagia than is warranted for any one symptom as a diagnostic point, but as a general rule we believe that it is safe to state that any patient in an endemic area with predominantly respiratory complaints associated with substernal pain on swallowing should be considered as coccidioidomycosis and properly investigated.

Assuredly, coccidioidal infection is potentially a fatal disease if dissemination occurs. The primary form, however, has appeared extremely mild, and with laboratory facilities to aid in suggesting the danger of dissemination, we do not believe it necessary to hospitalize these patients for longer periods than we have in our present series. Such follow-up studies as we have been able to carry out have substantiated this belief. We would emphasize, however, that each case must be treated according to its individual merits.

The significance of the positive Kahn test in two individuals, previously negative, and in one case previously treated but with subsequent negative reports, is questionable. Sweigert, Turner and Gillespie [10] report on four positive Kahns incidental to coccidioidal injection in their series of cases. We can merely confirm that this has occurred in our series as well, and mention it as an interesting finding which deserves further investigation.

Although we feel certain that we have seen at least 75 cases of coccidioidal infection, we have reported on only those which we felt were definitely confirmed. This, perhaps, accounts for the unusually high percentage of allergic skin manifestations in our series, as compared to the 2 to 5 per cent established by Smith.[5]

Coccidioidomycosis still remains a problem primarily for the physician of the endemic areas. To the physician elsewhere it undoubtedly will continue to have little significance as a primary concern in medical diagnosis. However, Kurz and Loud [11] have recently reported from New England the importance of the disease in interpreting chest films in individuals who have at any time resided in the endemic areas. Kundstadter and Pendergrass [12] have emphasized the possible pediatric problem which may arise in confusing childhood tuberculosis with acute, subacute, or healed coccidioidal infection. Clark and Gilmore [13] have also stressed the similarity in radiologic ap-

pearance of tuberculosis and persistent or slowly disappearing coccidioidomycosis and urge careful investigation.

We are of the opinion that coccidioidomycosis deserves a place in the differential diagnosis of any acute or chronic pulmonary infection for which an immediate cause is not apparent. Similarly, we feel that when abnormal shadows are noted on routine radiologic examination of the chest in any individual with a history of residence in an endemic area, the disease warrants consideration.

Summary

1. Observations on 43 cases of primary coccidioidomycosis are presented. These observations concern themselves with length and severity of exposure, symptoms, physical and laboratory findings, and subsequent follow-up studies.

2. The roentgen findings are classified and described according to types, and the frequency of incomplete resolution is mentioned.

3. The occurrence of dysphagia as an important diagnostic help is described.

4. Three cases in which positive Kahn tests developed incidental to coccidioidal infection are described.

5. The relative mildness of the disease and early symptomatic recovery of the patient are discussed.

6. Some knowledge of the nature of the disease is recommended for physicians both in and out of the endemic areas.

Photographic reproductions by Cpl. T. M. Roberts, Base Photo Laboratory.

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CASE REPORTS

ACUTE PORPHYRIA: REPORT OF TWO CASES WITH ELECTRICAL STUDIES IN ONE *

By Gustavus A. Peters, M.D., F.A.C.P., *Rochester, Minnesota*

Porphyria, although an uncommon disease, has been well described by such investigators as Günther,[1] Mason, Courville and Ziskind,[2] Watson,[3-5] Turner,[6] Waldenström,[7, 8] Dobriner and Rhodes,[9] Nesbitt [10] and Watkins,[11] and Welcker.[12] Oddly enough few medical textbooks discuss this interesting metabolic disease adequately or at all. However, as more cases are being reported the disease is becoming more generally known. Its early recognition would prevent unnecessary operative procedures and administration of contraindicated drugs, as well as lessen confusion with certain neuropsychiatric disorders.

There are two main types of porphyria, acute and congenital. They are considered to be due to an inborn error of metabolism but little is known regarding this metabolism. Acute porphyria has been classified as toxic or idiopathic depending on whether a causative agent is found.

The purpose of this paper is to report two additional cases of the acute idiopathic type. One patient had neurologic complications with residual symptoms, the other had none. Electrodiagnostic studies were done on the former, with the help of an electromyograph and a constant current impulse stimulator.[13, 14] The latter was devised by Golseth and Fizzell.[15] Dillon [16] has recently reported the use of this type of electrical test on peripheral nerve injuries and the interpretation of tetanus ratio, chronaxie, repetitive stimuli, strength duration curve in normal, regenerating, degenerating, and denervated states. The literature reveals few studies on electrical excitability of muscles in porphyria, and only one previous report so far as could be determined with the use of the electromyograph.[17] It was thought that such studies might be of some value in light of the postmortem findings reported by other investigators in cases of acute porphyria.

There seems to be no doubt that some product of the porphyrin metabolism can produce damage to the nervous tissue since involvement of peripheral nerves is seen so frequently. However in some cases of porphyria the nervous system is not involved. The presence of porphyrins in the sympathetic ganglia has been considered to be the cause of abdominal distress.[2] Porphyrins have been found in other tissues of the body, including the central nervous system and liver.[2, 18-20] This paper is concerned chiefly with the effect on peripheral nerves.

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Ross and Bury,[21] in 1893, noted that in porphyria with Landry's type of paralysis the electrical excitability of paralyzed muscles frequently remained unaltered. Grünewald,[22] in 1922, noted electrical reactions like those of myasthenia gravis in a case of porphyria with paralysis. Mason, Courville, and Ziskind [2] reported widespread and patchy degeneration of the myelin sheaths and axis cylinders in motor nerves. Palmer [18] reported a case of acute idiopathic porphyria with acute ascending paralysis. At necropsy he found marked degenerative changes in the liver and kidney, and in the myelin sheaths of the peripheral nerves. In certain parts of the nerves lymphocytic infiltration was present. Prior to death the patient had had bilateral ankle and wrist drop and ptosis of the left eyelid.

Baker and Watson [19] also described extensive changes in the peripheral nerves, chiefly in the median nerves, in the form of demyelinization and vacuolization. The most advanced changes were observed within the center of the nerve with the periphery keeping somewhat its normal architecture. In many regions the myelin sheaths were completely disrupted, leaving only faint outlines of globules as a residual of the destroyed tissue. The axones showed a wide range from swelling and color loss to a marked fragmentation and total disappearance. In the cervical anterior horn cells chromatolysis, swelling and neurologic changes were observed. Muscle fibers appeared to have lost their striations, normal staining properties, and there was a partial disappearance of the sarcolemma. Complete muscle degeneration was not observed, even though the patient had had the disease and had been under observation for about three years. Denny-Brown and Sciarra [20] in 1945 also recorded pathologic changes practically identical with those of Baker and Watson.

In a case reported in the *New England Journal of Medicine*,[17] quadriplegia developed and death from respiratory paralysis occurred 19 days later. At necropsy marked degenerative changes were found to have affected a large proportion of the nerve fibers. The myelin sheaths were swollen, constricted, incompletely divided into short segments, and in many instances broken up into round fragments. There were many fusiform enlargements and constrictions of the axis cylinders. The spinal cord showed axonal reactions of the anterior horn cells; namely, swelling of the cells and central chromatolysis of the Nissl substance. An electromyogram done on the fourth hospital day showed a low voltage, repetitive discharge in the left and right extensor carpi radialis, as well as in the left gastrocnemius muscle.

Muscular atrophy has been seen frequently as a sequel to porphyria. It is of interest to note the atrophy reported recently in the case of Halpern and Copsey [23] and DiFiore.[24]

Yeager [25] has recently presented a close diagnostic differentiation between the neuritis of porphyria and of Guillain-Barré syndrome; he emphasized the involvement of motor nerves and poor prognosis in the former in contrast to motor and sensory nerve involvement and fairly good prognosis in the latter. This disease is emphasized in differential diagnosis because it is not infrequently confused with acute porphyria as illustrated in my second case. In one of Hoagland's [26] cases of acute porphyria Guillain-Barré syndrome was suspected at first.

Case Reports

Case 1. The patient was admitted to Ashford General Hospital, White Sulphur Springs, on February 24, 1946. He was 30 years of age, unmarried and a veteran of World War II, who had been discharged January 28, 1946. He had entered the service in January, 1942, and while in the Army had visited the dispensary only four times because he had difficulty in holding his urine while sitting in lectures or shows. Nothing abnormal was ever found in the urine, and during those four years he had never been hospitalized.

On admission, the patient complained of pain in the abdomen and back, aching in the arms and legs and much fatigue. He stated that on February 20, 1946, he had shoveled about six tons of coal from a truck into a basement, and on the following day he awoke early with severe abdominal pain. Two days later he had not improved in spite of treatment at home; the abdominal and back pain continued, and he felt feverish for the first time. Hospitalization was advised. He vomited twice on this day, had frequency of urination, about 15 to 20 times, which lasted one day. There was no dysuria and no abnormal color of the urine.

The family history was negative. The past personal history was also noncontributory. He had had measles, mumps and chickenpox.

On examination in the hospital the patient was moderately apprehensive and nervous and did not appear acutely ill. He was 5 feet 11.5 inches tall (182 cm.) and weighed 145 pounds (65.8 kg.). There was telangiectasis on both cheeks. The gums bled easily. The pulse while he was sitting was 108 beats per minute and blood pressure in millimeters of mercury was 160 systolic and 90 diastolic. Tachycardia was noted. The liver and spleen were not palpable. The muscle tone and the grip in both hands and strength of the muscles of the lower extremities and the neck were good. Generalized tenderness was elicited throughout the abdomen. On examination of the genitalia pink stains were found on the patient's underclothing. The patient stated he had never observed similar stains before. A specimen of urine was obtained, and it was found to be pink, which turned to a darker red on exposure to light. A test for porphyrins gave positive results, and a provisional diagnosis of acute porphyria was made, after the fifth day of hospitalization. During the first four days in the hospital a presumptive diagnosis of ulcer was made because of blood-tinged vomitus. Treatment consisted of a bland diet and antispasmodic drugs, codeine sulfate, phenobarbital, and pentobarbital sodium until the diagnosis was established.

Tests revealed the urine to contain coproporphyrin and uroporphyrin, the latter in the amount of 0.4 mg. per 100 c.c. of urine. A positive test was obtained for porphobilinogen. The patient's temperature rose to 102° F., but fell to 99.2° on February 25, 1946. On February 26 erythrocytes numbered 4,130,000 per cubic millimeter of blood, a sedimentation rate on two occasions was 3 and 11 mm. for the first hour, and the hematocrit reading was 40 and 42 on two occasions also. Serial electrocardiograms revealed a broadening of and dome-shaped T-waves with a prolonged Q-T interval at the height of illness. It was the opinion of the cardiovascular consultant that the patient had an acute hypertension secondary to the acute porphyria. He also noted a violaceous discoloration of the exposed and acral portions of the ears, elbows, shoulders and malleoli. Examination of the eye revealed normal ocular fundi. Neurologic examination was negative, no abnormal reflexes being present. The abdominal reflexes were hyperreactive, and there was no muscular paralysis or atrophy. Cystometric examination revealed evidence that the capacity of the bladder was normal. Proctoscopic examination was negative. Roentgenograms of the lumbosacral portion of the spinal column, of the upper part of the gastrointestinal tract and the colon and the chest were all negative.

This patient made a fairly rapid recovery and was dismissed from the hospital

in six to eight weeks. No electrical tests were performed since there were no neurologic complications.

Case 2. This patient, an army nurse 25 years old, who had seen two years of service was admitted to Percy Jones General Hospital on November 22, 1946 because of Guillain-Barré syndrome. On the trip to the Southwest Pacific theater in 1945 she sustained a severe sunburn on one occasion. Later an upper respiratory infection developed and continued for about a month. This was followed by weakness, anorexia, malaise and an aching of the midabdominal region, with severe lancinating pains around the lumbar region, which later progressed down both legs. Sweating increased in the lumbar region and progressive weakness was noted in the right arm, forearm and hand. The patient was hospitalized on October 3 for 17 days. Her condition was considered an anxiety reaction, and she was told she would be all right as soon as she became accustomed to army life. She asked to go back to duty to avoid the neuropsychiatric consultant with whom she disagreed, even though muscular weakness had begun in her upper extremities and both thighs and hips felt numb. Saddle anesthesia was present for seven to 10 days. She could feel pressure, but no pain. Before her dismissal she was unable to raise her right arm above her head.

Four days after her return to duty she was admitted to another hospital in the Philippine Islands because she was unable to do such simple things as manipulate a hypodermic syringe and was weak and trembling after any activity. Blood pressure was 120 mm. of mercury systolic and 95 diastolic. The pulse rate varied from 124 to 84, with an average of about 90 beats per minute. Her deep reflexes were active and equal; the superficial reflexes were normal. Neurologic examination revealed 75 per cent paralysis of the left deltoid muscle, 100 per cent paralysis of the right deltoid muscle, 25 per cent weakness of the pectoral muscles and 75 per cent weakness of the biceps muscles bilaterally. About 25 per cent atrophy was noted in the muscles of the right shoulder girdle. She had some difficulty in swallowing and breathing in the initial stages of the disease. A diagnosis of infectious neuronitis of the fifth and sixth cervical segments was made. About November 1 facial palsy developed. The patient was transferred by air to the United States on November 10, 1945.

In the States quadriplegia was noted. She could not walk or use her upper extremities. She could not sit up without assistance, or wrinkle her forehead, and her facial expression was flat on the right side. Her ability to cough and speak was considerably impaired. She complained of severe pain in her extremities. She was unable to close her eyes completely. The abdominal reflexes were intact. All reflexes in the upper extremities were absent. No sensory changes were noted. Function returned to the lower extremities fairly rapidly, but the knee reflexes were absent. The ankle jerks were present and active. On November 22, 1945, her blood pressure was 130 systolic and 94 diastolic. Her pulse rate was 100. About December 10 she began to walk with assistance and by December 28 she was able to lift her hands. All laboratory tests, including analysis of spinal fluid, gave negative results except for a slight diminution in erythrocytes and hemoglobin in the blood. The diagnosis of infectious neuronitis or Guillain-Barré syndrome was concurred in.

Between February 26 and November, 1946, when she entered the Percy Jones General Hospital this patient was admitted to four additional hospitals with the diagnosis of Guillain-Barré syndrome. Spinal fluid was essentially normal on two occasions except for an elevation of protein to 58 mg. per 100 c.c. at one time. Her condition gradually improved, but three exacerbations, in the spring, summer and fall, interrupted the steady progress. The exacerbations were characterized by part or sometimes by all of the following symptoms: slight fever; anorexia; weakness; loss of weight; occasional nausea and vomiting; generalized abdominal tenderness; girdle-like abdominal pain; pain in the lower extremities; tachycardia and hypertension.

Usually there was a prodromal period of malaise and vague complaints which the patient referred to as "a cold." At one hospital, which she entered because of a "cold" and fear of another recurrent attack, analysis of urine disclosed a dark red-amber color. During the second exacerbation opiates had to be used to control severe muscular aches. Use of these was continued off and on until December, 1946. In October, 1946, the patient's mother, who apparently had had hypertension for some time, died from a cerebrovascular accident.

At the time of admission to the Percy Jones General Hospital the patient was having her second episode of saddle anesthesia which lasted about 10 days. Her complaints were severe aching and weakness of the upper and lower extremities, and especially about the shoulders, arms and hands.

The family history was not significant. The patient had had the usual childhood diseases, influenza and five years previously an appendectomy. She stated that the pain in her attack of appendicitis was a little unusual because it was located on both sides of her abdomen and extended downward in a V formation. No exposure to toxic agents was found. Her menstrual periods had been irregular and amenorrhea had existed since October, 1946.

Physical examination on admission revealed marked weakness and atrophy of the muscles of the shoulder girdles, arms, forearms and hands, more marked on the right than on the left, a pronounced weakness and clumsiness in the use of her hands with practically useless thumbs and atrophy of the muscles of the back. The legs appeared normal. Many muscle groups were tender and aching. A slight facial weakness was noted. The deep reflexes were equal and within normal limits bilaterally. No sensory disturbance other than hyperesthesia about the arms was noted. Her blood pressure was 108 mm. systolic and 78 diastolic. The heart rate was normal. The liver and spleen could not be palpated.

On January 4, 1947, further examination was carried out. At this time the patient did not appear acutely ill and weighed 105 pounds (47.6 kg.). Obvious atrophy of the muscles of the shoulder girdles and of the upper extremities, a residual of her former facial paralysis and a lid lag on the left were present. No nystagmus was noted. The gag reflex was present and hyperactive. No impairment of sensation was found. Babinski's and Romberg's signs were negative. The knee jerks were diminished, while the ankle jerks were lively and equal bilaterally. Abdominal reflexes were present in the upper quadrants. The biceps tendon reflexes were diminished, and the triceps tendon reflexes were not elicited. Both upper extremities were weak; the right was the weaker. The patient was able to abduct the left shoulder to 90 degrees, the right only about 20 degrees. She was hardly able to flex the right elbow enough to get the right hand to her mouth. As a matter of fact, she was just barely able to overcome gravity and flex the elbow from 180 to 45 degrees. The patient found it difficult to get up from a supine position. She managed it, by turning on her right side, and using her left upper extremity to push herself up to a sitting position. Her teeth were definitely discolored and contrasted markedly with two false teeth which had matched the other teeth perfectly in color two years previously.

About six weeks later the patient was able to abduct and elevate her upper extremities as shown in figure 1. Her hands, however, failed to show improvement (figure 2). She was unable to dress or put up her hair. The strength of the lower extremities was found to be within normal limits and equal bilaterally.

Laboratory tests in January, 1947: Erythrocytes numbered 5,170,000 and leukocytes 12,000 per cubic millimeter of blood. There was 14.0 gm. of hemoglobin per 100 c.c. of blood. A differential count showed 61 per cent neutrophiles, 3 per cent eosinophiles, 2 per cent basophiles, 9 per cent monocytes, and 25 per cent lymphocytes. The Kahn test was negative for syphilis. The urine was a pale amber

FIG. 1. (case 2). Atrophy and weakness in shoulder girdle muscles with muscle substitution and resultant cervicodorsal scoliosis. (Picture was taken in recovery phase.)

color and contained three to five leukocytes and 12 squamous epithelial cells per high-power field. Its specific gravity was 1.005.

Tests of the blood showed concentrations of 4.3 mg. of phosphorus and 9.4 mg. of calcium per 100 c.c. of serum, 20 mg. of urea, 1.7 mg. of creatinine, 83 mg. of sugar per 100 c.c. of blood and 480 mg. of chlorides and 240 mg. of cholesterol per 100 c.c. of plasma. Her basal metabolic rate was −9 per cent. Cephalin flocculation and bromsulfalein tests of liver function gave negative results. Analysis of spinal fluid showed no cells, a negative Wassermann reaction, a gold curve of

FIG. 2 (case 2). Patient's hands on left. A normal hand on right. Atrophy of muscles of the thenar eminences of patient's hands, especially of the patient's left hand. Both thumbs of patient demonstrate marked atrophy and loss of strength by their extreme lateral and flat position. Contrast with normal hand on extreme right.

0000000000, and a total protein of 50 mg. per 100 c.c. with a faint trace of globulin. Gastric analysis (histamine) showed free hydrochloric acid present. Roentgenograms of the chest and cervical portion of the spinal column revealed no abnormalities.

Because the urine at the time of one of the urinalyses, in another hospital, was a dark red amber, a specimen of urine was exposed to ultraviolet light. It became pinkish after five minutes' exposure. A test of urine for porphobilinogen gave a positive reaction. Quantitative analyses of the urine, done through the courtesy of Dr. Samuel Nesbitt, University of Minnesota, revealed 254 and 90 gammas of coproporphyrin and 1,574 and 5,270 gammas of uroporphyrin, respectively, in two 24 hour specimens. A third specimen of urine contained 219 gammas of coproporphyrin and 13,400 gammas of uroporphyrin. Spectroscopic analyses, done at the University of Michigan through the courtesy of Dr. Charles Wilkinson, Jr., revealed absorption bands at about 590 to 600 and 540 to 550 millimicrons when the urine was extracted with acetic acid and ether, according to the method of Dobriner and Rhoads. This finding would indicate the presence of uroporphyrin III. This same urine was examined with the Evelyn photo-electric colorimeter with the 420 filter, and gave a quantitative yield of coproporphyrin (ether soluble) of 10 gammas per 100 c.c., or 125 gammas for the entire volume. When examined with Beckman's spectrophotometer, this extract gave a strong absorption band at 400.

The patient was found to be somewhat hypersensitive to ultraviolet light, but not greatly so. Hyperemia was the chief effect. The dosage, however, was kept low.

Evaluation of muscle strength and electrodiagnostic studies.—Voluntary muscle tests taken in November, 1946, January and February, 1947, showed improvement in strength in the trapezius, rhomboidei, latissimus dorsi, pectoralis major, teres major and minor, infraspinatus, supraspinatus, biceps, triceps, deltoids, brachioradialis, extensor carpi ulnaris, palmaris longus, flexor digitorum sublimis and profundus, flexor pollicis longus, flexor carpi ulnaris, interossei dorsales and abductor digiti quinti muscles bilaterally. No improvement in strength or recovery of muscle power was noted during the same interval in the extensor digitorum communis, abductor and extensor pollicis longus, extensor flexor and abductor pollicis brevis, flexor carpi radialis, opponens and adductor pollicis, lumbricales and opponens digiti quinti bilaterally.

Reaction of degeneration was observed mainly in the muscles of the right thenar eminence and the left extensor digitorum longus. Evidence for this type of reaction was seen in the lack of response to faradic stimulation and a slow muscular contraction to galvanic current. No fibrillation of the muscles was observed, but flipping the little finger of the right hand would sometimes set the intrinsic muscles into spasmodic contractions. At times involuntary contractions of the muscles of the shoulder girdles were observed.

Electrodiagnostic data obtained by Capt. E. L. Dillon, M.D.P.T., from the abductor pollicis brevis and extensor digitorum communis of both upper extremities are listed in table 1. The constant current impulse stimulator devised by Golseth and Fizzell and an electromyograph were employed. The galvanic current was used in an interrupted fashion as was the faradic current. In the case of the repetitive stimuli three variances were used, namely 77, 166, and 500 stimulations per second. To determine the galvanic tetanus ratio a stimulus of one and a half seconds' duration with a time interval of four seconds was used.

These studies revealed a loss of response of the muscles to faradic stimulation, lengthening of the chronaxie at the time of first examination with slight decrease on subsequent examinations, loss of normal response to repetitive stimuli, and slight changes in the galvanic tetanus ratios. This evidence indicated diminution and loss of voluntary power in the atrophic muscles. The muscles which were involved followed no definite distribution, but instead presented a patchy pattern. All muscles of

TABLE I

Electrodiagnostic Data from Abductor Pollicis Brevis and Extensor Digitorum Communis Muscles

	Voluntary Muscle Test*	Response to Stimulation†		Strength Duration Curve	Chronaxie	Repetitive Stimuli	Galvanic Tetanus Ratio	Electromyographic Studies	Atrophy
		Galvanic	Faradic						
Extensor digitorum communis Right Jan. 10, 1947	0	3	0	Continuous	40	Overflow‡ at 14.0 ma.	4.2	Monophasic and polyphasic motor units	Yes
Feb. 25	0	3	0	Continuous	29–40	Overflow at 9.0 ma.	2.6	Monophasic units	Yes
Left Jan. 10	15	3	0	Continuous	20	No tetanus at 11.5 ma.	3.8	Low voltage and low amplitude polyphasic motor units	Yes
Feb. 25	15	2	0	Continuous	20	8.5 ma. Overflow at 12.0 ma.	3.6	Polyphasic and monophasic motor units	Yes
Abductor pollicis brevis Right Jan. 10	0	2	0	Continuous	40	Overflow at 4.5 ma.	4.2	High voltage monophasic motor units	Marked
Feb. 25	0	2	0	Continuous	29–40	Unable to tolerate	2.5	High voltage monophasic motor units	Marked
Left Jan. 10	0	3	0	Continuous	14–20	Overflow at 9.2 ma.	4.3	Low voltage monophasic motor units	Marked
Feb. 25	0	3	0	Continuous	29–29	Overflow at 12.8 ma.	3.1	Low voltage monophasic motor units	Marked

* 0 = no contraction; 100 = normal contraction.
† 4 = normal response; 0 = no response.
‡ Overflow denotes spread of current to adjacent muscles.

the radial, ulnar and median nerves bilaterally, as well as practically all muscles had, at one time or another, shown a complete loss of or diminution in power. This was most marked in the intrinsic muscles of the hands and the muscles below the elbows supplied by the radial nerve. Atrophy was most marked in the thenar eminences, but was evident in both entire upper extremities. Associated with the atrophy in the muscles of the thenar eminences was the presence of resistance suggesting fibrosis. This fibrosis was discovered when the electromyograph needles were introduced into the muscles of the thenar eminence. Electromyographic studies did not reveal the presence of true fibrillation. Motor units of the monophasic and nascent polyphasic type were observed. The latter type could indicate regeneration although degeneration is not excluded while the former suggests a more normal type of motor unit, especially if the electropotentials are high. Various types of motor units were obtained, ranging from a low voltage polyphasic type to high voltage monophasic type. Squeaking was noted in some muscles, which would indicate that regeneration might be taking place.

No change or only slight change occurred in voluntary power in these muscles from January 10 to February 25, and there was not any change in the response to faradic current or to galvanic current. The strength duration curves showed no discontinuities. There was little change in chronaxie. Repetitive stimuli revealed that the muscles did not react normally, inasmuch as considerable milliamperage was necessary to obtain tetanus, and it could not always be obtained. The galvanic tetanus ratio showed a gradual reduction in the six weeks between tests. This would appear on first glance to indicate a regression in the status of the affected muscles. Actually the findings are within normal limits of neurotization, and probably represent a different group of and more poorly neurotized muscle fibers than those which were tested the first time.

Treatment and Results. Hydrotherapy, electrical stimulation to the muscles which would not react voluntarily, and reëducational and strengthening exercises were employed. In addition, occupational therapy, in the form of handicraft that necessitated coördination and movements of the hands and fingers, was prescribed. The patient felt that this treatment not only improved her condition, but kept her from regressing. She was advised to use a liberal diet high in calories and vitamins, and to keep her nutritional state up to a high level, and was encouraged to put on weight. She did improve in general body strength, which was definitely noticeable in the upper extremities and shoulder girdles. The facial weakness and lid lag diminished to such an extent that they could scarcely be recognized. In February, 1947 she had a short, mild episode of muscular aches and pains in her extremities. She was discharged from the service, and the last word on her condition (December, 1947) was that she had improved enough to write legibly, but movement of the thumbs was still poor. Otherwise, she had recovered.

Comment

It is of interest that porphyria in case 2 had passed as a Guillain-Barré syndrome for approximately 15 months and remained unrecognized in nine different hospitals. In contrast, the condition in case 1 was recognized within the first week that the patient was hospitalized. The feature which led to the diagnosis was the reddish discoloration of the patient's underclothing. However, until the real diagnosis was established, peptic ulcer was thought to be present. The symptoms of abdominal pain characteristic of porphyria have frequently led to surgical exploration, but fortunately these two patients were spared. The case of Halpern and Copsey illustrates how porphyria can simulate coronary occlusion and acute intestinal obstruction, the latter leading to surgery.

Porphyrins apparently cause a spasm of smooth muscle for contraction of the intestinal wall has been observed at operation and spasm of retinal arteries has been seen on funduscopic examination. Denny-Brown has said that the pathologic findings could be those associated with ischemia due to intense arteriolar spasm. The effect of arteriolar spasm would be diffuse and extensive; there would be headaches, hyperactive knee jerks, nystagmus, convulsive seizures, hallucinations, somnolence and motor paralysis. Due to the intense arteriolar spasm, the ischemia which results produces degeneration of myelin sheaths and destruction of axis cylinders, if severe. Just why the motor nerves are involved more than the sensory, and why in a patchy way, has not been explained. Nor is it possible to explain why in case 1 there were no neurologic complications, although the urine was red, and in case 2 extensive involvement of the nerves was present although the color of the fresh urine was essentially normal.

Electrodiagnostic data obtained in case 2 are compatible with what other investigators have found at necropsy, namely, that the disease strikes the peripheral nerves, especially the motor component, in a patchy manner. The nerves were sufficiently damaged to produce a reaction of degeneration and abnormal motor unit patterns. Residual atrophy of the muscles was grossly evident over the body, more so in the shoulder girdles and upper extremities, and especially in the small muscles of the hands. Fibrosis was definite in these latter muscles also. Fibrillation was not observed. Its presence would have indicated complete denervation. The fact that it was not observed would suggest that innervation, although poor in the muscles most affected, was not completely cut off. No muscles were found which did not respond at least to galvanic stimulation. Most of the electrodiagnostic data were compatible with that seen in regenerating peripheral nerve injuries.

Clinically the effects on the neuromuscular system did not appear necessarily irreversible in case 2. Some of the muscles probably will never return to normal, but it appeared that many muscles, although they had lost a considerable amount of power, had recovered to an almost normal state. The patient in case 2 was paralyzed in all four extremities at one time, and even had difficulty in breathing and talking. After being bedridden she recovered so that she could again walk, and partially use her arms and fingers. Her thumbs, though, have remained practically useless. The intrinsic muscles of the hands appear to have been affected most permanently, especially those of the thenar eminences. It is logical to assume that, if atrophy occurs in these small muscles, and is present for some time, that a return to a normal condition would be very slow, if at all. The electromyographic findings are in keeping with the postmortem findings reported in other cases of acute porphyria, in that certain motor units were found either in a degenerative or regenerative phase, while others were found in an essentially normal stage, or were intermediate.

Summary

Two cases of acute idiopathic porphyria have been reported. One was easily recognized by the characteristic red urine. The other case passed as a case of Guillain-Barré syndrome for more than a year, chiefly because the urine was essentially normal in color when voided. Both cases were characterized during their attacks by acute abdominal symptoms, tachycardia and hypertension. In

one of the cases neurologic complications in the form of muscular paralysis (quadriplegia), bulbar symptoms in the form of dysphonia and dysarthria were noted, but the patient eventually made an almost complete recovery. Muscular atrophy and paralysis persisted in the upper extremities and shoulder girdles. The radial and median nerves were most affected.

Data from electrodiagnostic tests by means of a constant current impulse stimulator and an electromyograph were compatible with postmortem pathologic findings of patchy degeneration of motor nerves. No evidence of complete degeneration was obtained, although there was some evidence of regeneration. Return of voluntary power was noted in some muscles. Muscles which were weakened showed gradual improvement in strength as the disease was allayed and as they were encouraged to further activity.

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HYPERSPLENISM: TWO CASES WITH LEG ULCERS TREATED BY SPLENECTOMY *

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SPLENOMEGALY is the common factor in a variety of syndromes of indefinite etiology in which leukopenia, anemia, and thrombocytopenia may be associated disorders. Splenomegaly and leukopenia in rheumatoid arthritis are well known under the name of Felty's syndrome. Chronic leg ulcers have frequently been described in splenomegalic syndromes, and we have recently encountered two cases presenting splenomegaly, atrophic arthritis, anemia, elevated basal metabolism rates, leukopenia with relative and absolute neutropenia, and chronic nonhealing leg ulcers.

CASE REPORTS

Case 1. A 59 year old white male entered the hospital on April 2, 1945 complaining of an ulcer on the right shin which had been present for approximately one year. The lesion had first appeared spontaneously as a brownish-red papule which increased in size but did not ulcerate. Five months before admission, the lesion had been excised and promptly healed. However, one month before admission an extremely painful ulcer appeared in the area of excision, making it impossible to bear weight on the extremity. Healing did not follow local application of bland ointments. In addition to this complaint, there had been a crippling arthritis of the hands and "heart attacks" of an indefinite nature, both of approximately 15 years' duration.

Examination. The patient was a thin, pale man who appeared chronically ill. Blood pressure was 148 mm. Hg systolic and 90 mm. diastolic; pulse, 120; respirations, 18; temperature, 99.0° F.; weight, 130 pounds. Abdominal examination revealed a prominently enlarged spleen; there was no hepatomegaly. Examination of the extremities revealed ankylosis of the phalangeal joints of the fingers and toes, with atrophy of the overlying skin, prominence of the joints, and ulnar deviation of the fingers (figure 1). On the anterolateral aspect of the lower portion of the right

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leg there was an ulcer measuring 6 by 7 cm. with a black necrotic base surrounded by an area of redness and induration. There was no peripheral edema, and the feet were warm, with reduced but equal peripheral pulses on the two sides. There was no peripheral lymphadenopathy. A few small varicosities were observed in both lower extremities, but the deep venous return was unimpaired.

Admission urinalysis showed a faint trace of albumin, a specific gravity of 1.019, no sugar, and occasional coarse granular casts in the sediment. Hemoglobin was 11.2 gm. (71 per cent); red blood cell count, 3,857,000, and white blood cell count, 3,750, with a differential of 52 per cent segmented neutrophiles, 45 per cent lympho-

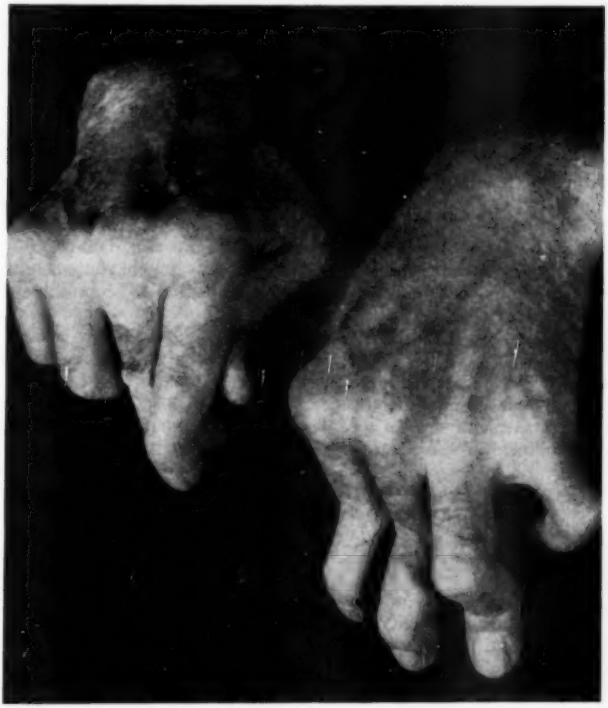

FIG. 1. *Case 1.* Note extensive crippling arthritis.

cytes, and 3 per cent monocytes. Hypochromia of the red cells was noted in the smear. Non-protein nitrogen content was 19 mg. per cent; total serum protein, 6.1 gm. per cent, with an albumin of 2.9 gm. per cent, and a globulin of 3.2 gm. per cent. The prothrombin amount varied between 87 per cent and 108 per cent of average normal. The platelet count was 350,000; bleeding time, 5 minutes, and clotting time, 3 minutes. Basal metabolism rate was plus 45. Reticulocyte count was 5 per cent. The blood Kahn reaction was negative.

Repeat white blood cell counts varied between 2,250 (April 7), 825 (April 10), 1,800 (May 8), and 2,250 (July 7, 1945), the differential for the white blood cell

count of 825 showing 2 per cent immature myelocytes, 2 per cent juveniles, 3 per cent stabs, 28 per cent segmented neutrophiles, 43 per cent lymphocytes, 5 per cent abnormal monocytes, 9 per cent immature monocytes, 5 per cent monocytes, and 3 per cent eosinophiles.

A roentgenogram of the chest showed a slight increase in the linear and hilar markings and an old scarring at the right apex. A film of the right leg showed calcification of the tibial vessels, cortical thickening, and increased cortical density underlying the ulcerated area. Arthritic changes were noted in the joints of the knees, wrists, hands and digits, with areas of diminished bone density and narrowing of the joint spaces.

Course. Three biopsies of the leg lesion revealed acute and chronic inflammation. A sternal bone marrow biopsy showed innumerable nucleated red cells, many cells of the myeloid series in various stages of transition, and focal areas of mature and immature myelocytes. There was no evidence of leukemia. The hemoglobin and red blood cell count responded poorly to transfusion, and because of auto-agglutination, difficulty was encountered in the administration of blood. The lesion did not respond to débridement, and following numerous transfusions (on the presumptive diagnosis of aleukemic leukemia) roentgen therapy was given over a period of eight days without improvement. Subsequent to this therapy, the ulcer was débrided on two other occasions, followed by frequent dressings and mechanical cleansing, and roentgen therapy to the leg lesion was given over a period of 11 days, again without appreciable improvement. The lesion began to evidence slight infection, and 10,000 units of penicillin were given parenterally every three hours. A cephalin cholesterol flocculation test was 4 plus, and there was 15 per cent retention of bromsulfalein after 30 minutes.

In spite of these measures, the ulcer progressively enlarged and the patient gradually lost eight pounds weight. The white blood cell count remained persistently low, and lymphocytes predominated at the expense of a reduction in the granulocytic series.

On the sixty-fifth hospital day (June 20, 1945) a 1,540 gm. purplish-gray spleen was removed. The splenic vessels appeared normal, and samples of blood taken from them gave the following determinations:

Blood from Vein		*Blood from Artery*	
Hemoglobin 12.9 gm. 82%		Hemoglobin 13.8 gm., 88%	
Red cell count 4,560,000		Red cell count 5,000,000	
White cell count 670		White cell count 825	
Differential:		Differential:	
Myeloblasts	0%	Myeloblasts	1%
Myelocytes	5%	Myelocytes	5%
Juveniles	7%	Juveniles	0%
Stabs	16%	Stabs	17%
Segmented neutrophiles	16%	Segmented neutrophiles	30%
Lymphocytes	54%	Lymphocytes	36%
Monocytes	2%	Monocytes	5%
Basophiles	0%	Basophiles	2%
Platelets 180,000		Platelets 280,000	

Microscopic examination of the spleen showed slight congestion but no evidence of leukemia, amyloid disease, Hodgkin's disease, or any specific inflammatory processes. There was an increase of plasma cells and of nucleated red cells, but no increase in connective tissue and no phagocytosis of white cells. The changes observed were interpreted as being consistent with chronic infection of long duration.

Postoperatively, the patient's temperature rose to 100.6° F. on one occasion, but otherwise it did not go above 100.0° F. A minimal atelectasis of the right upper chest was transitory, and an epididymitis responded to roentgen therapy. A white count on the second postoperative day was 17,800; on the fifth day it was 5,800 with a differential of 3 per cent juveniles, 27 per cent stabs, 63 segmented neutrophiles, 6 per cent lymphocytes, and 1 per cent monocytes. The sixth and seventh days leukocyte counts were similar. Subsequently the white blood cell count varied between 1,400 and 3,700 with an average of 30 per cent to 40 per cent stabs, 20 per cent to 30 per cent segmented neutrophiles, and 20 per cent to 35 per cent lymphocytes. Prothrombin content remained above 75 per cent of average normal, and gradually increased to 93 per cent.

Following splenectomy, the ulcer improved rapidly under wet dressings and mechanical cleansings, and pinch grafting was successfully accomplished. (Prior to splenectomy, attempts at grafting could not be considered.) At discharge on the thirty-fourth postoperative day, the hemoglobin was 13.1 gm. (83 per cent); red blood cells numbered 4,362,000, white blood cells, 2,900, with a differential of 24 per cent stabs, 19 per cent segmented neutrophiles, 47 per cent lymphocytes, 2 per cent basophiles, and 8 per cent eosinophiles. Basal metabolism rate was plus 22.

Four months after discharge from the hospital (October 24, 1945) the patient was readmitted for extensive study, evidencing a weight gain of 35 pounds and striking improvement in his color and general appearance. The leg ulcer was completely epithelialized. There was no pain, and no confinement to bed. Urinalysis still showed a trace of albumin; the non-protein nitrogen content was 22 mg. per cent; total protein, 7.0 gm. per cent, with an albumin of 4.5 gm. per cent, and a globulin of 2.5. The hemoglobin was 15.4 gm. (98 per cent); red blood cells numbered 4,850,000; white blood cells 3,100; juveniles, 16 per cent; stabs, 8 per cent; segmented neutrophiles, 2 per cent; lymphocytes, 60 per cent; and eosinophiles, 14 per cent. The prothrombin amount was 81 per cent of average normal; basal metabolism rate, plus 15; and platelet count, 120,000. A cephalin cholesterol flocculation was three plus, and there was no retention of bromsulfalein after 30 minutes. Reticulocyte count was 1.2 per cent. Sternal marrow biopsy showed questionable slight hyperplasia with a questionable increase in the erythroblastic elements and some increase in plasma cells. These findings were essentially the same as before splenectomy. Following these studies, the patient was discharged.

Two months later, December 23, 1945, he was again admitted to the hospital, this time with two zones of ulceration within the area of pinch grafting. These nonpainful lesions had become manifest shortly after sequestration of a small bone fragment, and resembled in appearance those seen on the first admission.

Laboratory studies at this admission revealed a blood count of: hemoglobin, 13.4 gms. (85 per cent); red cell cells, 5,280,000; white cell cells, 2,850; juveniles, 1 per cent; stabs, 2 per cent; segmented neutrophiles, 8 per cent; lymphocytes, 61 per cent; monocytes, 26 per cent; and eosinophiles, 2 per cent. Platelet count was 200,000. Bleeding time was 35 seconds; clotting time, 3½ minutes. The reticulocyte count was 0.1 per cent. Urine showed a trace of albumin, no sugar, a specific gravity of 1.016, and numerous red cells and occasional hyaline casts in the sediment. Basal metabolism rate was plus 24; icteric index, 5; non-protein nitrogen content, 18 mg. per cent; total protein, 8.4 gm. per cent, with an albumin of 3.7 gm. per cent, and a globulin of 4.7. Cephalin cholesterol was 4 plus, and there was no bromsulfalein retention after 30 minutes.

Roentgenograms of the leg again showed cortical thickening and a small amount of periosteal proliferation. The sternal bone marrow showed no change from the preceding biopsies. A biopsy of the calf muscle on the affected side was normal. A high saphenous vein ligation and retrograde injection were performed at this admis-

sion, although no great benefit was anticipated. Fifteen days following admission, he was discharged.

At the fourth admission two months later the ulcers of the leg had coalesced, and the total area now measured 7 by 8 cm., an increase in size since the previous admission (figure 2). Laboratory determinations were similar to those of the previous admissions except that the urine was free of albumin and the sediment was negative. A roentgenogram showed a slight increase in the periosteal reaction previously noted. The patient's general condition was poor, and in truth he was in much the same state as when first seen. He was discharged after five days of hospitalization.

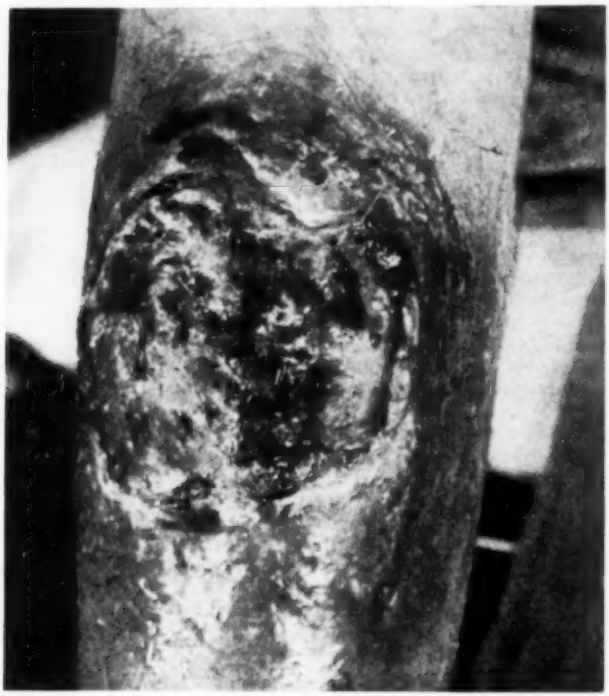

FIG. 2. *Case 1.* Area of extensive ulceration with infection eight months following splenectomy. Note complete failure of healing.

One and one-half months later, on April 6, 1946 (one year following the first examination, and 291 days following splenectomy) the patient died at his home. The family physician reported that the patient developed increasing infection and extension of the ulcer of the leg, with hemorrhage from that area. Frequent epistaxis and coughing up of blood suggested a bleeding tendency. In addition, the patient ran a high temperature and developed a throat infection. Permission for postmortem examination was not obtained.

Case 2. For eight months previous to entry on April 13, 1945, this 50 year old white female had an ulcer on the left leg, which (without antecedent trauma) had

first appeared as a small red spot. Coal oil and bland salve were applied, but small blisters appeared about the reddened area and the patient then consulted her family physician, who treated the lesion by cleansing and débridement of the blisters. In spite of this, an ulceration formed which gradually increased in size. There was also a history of deforming arthritis of 10 years' duration resulting in ankylosis of the finger and knee joints, progressive weakness concomitant with 12 pounds weight loss, and increasing nervousness and insomnia during the two months prior to admission. Family history and past history were noncontributory.

Examination. The patient was a thin, undernourished woman with evidence of weight loss. Blood pressure was 90 mm. Hg systolic and 52 mm. diastolic; pulse, 80; respiration, 18; temperature, 101.2° F., and weight, 87 pounds. The thyroid was thought to be slightly enlarged, but no bruit was heard. The left diaphragm was elevated. The heart was of normal size and shape, the rhythm regular, and a rough, blowing systolic murmur was heard at the apex and transmitted to the axilla.

FIG. 3. *Case 2.* Advanced atrophic arthritis. Note similarity to Case 1.

Abdominal examination revealed an enlarged spleen in the left upper quadrant, extending well below the level of the umbilicus. The liver was also slightly enlarged to palpation. There was no peripheral lymphadenopathy. A fixed flexion deformity of the knees was present, and the fingers showed ulnar deviation, flexion, and ankylosis, with prominence of the phalangeal and metacarpophalangeal joints (figure 3). On the lower third of the left leg a huge, necrotic, malodorous ulceration was observed, which was almost completely annular and measured 16 cm. in diameter. The edges of this lesion were slightly raised, the base black and secondarily infected, and there was little induration but considerable redness surrounding the ulceration (figure 4). There were no varicosities of either extremity; the right dorsalis pedis pulse was present, but a pitting edema of the left foot obscured the pedal pulse. Pelvic and rectal examinations were not unusual.

Admission blood work revealed a hemoglobin of 5.9 gm. (37 per cent), red cell count, 2,310,000; white cell count, 3,600; 4 per cent juveniles; 22 per cent stabs; 42 per cent segmented neutrophiles; 25 per cent lymphocytes; 5 per cent myelocytes;

1 per cent monocytes, and 1 per cent eosinophiles. On smear, the red cells showed marked hypochromia. Non-protein nitrogen was 14 mg. per cent, and total serum protein was 7.7 gm. per cent, with an albumin of 3.0 and a globulin of 4.7. A trace of albumin was found in the urine. The blood Kahn reaction was negative. A fasting blood sugar was 88 mg. per cent; basal metabolism rate was plus 80; urine examined for Bence-Jones protein was negative, and a blood culture was also negative. A culture from the ulcer showed unidentified spirochetes and gram positive cocci occurring in clusters and short chains.

A radiograph of the chest showed elevation of the left diaphragm, small calcified areas in the hilar regions, and somewhat thickened linear markings. Roentgenogram of the left leg showed demineralization and slight periosteal proliferation along the posteromedial aspect of the distal third of the tibia, and films of the knees and hands showed thinning of the joint spaces, with complete obliteration of some of the joints of the hands. Flexion deformities were noted in the digits, and demineralization of bone was present throughout. The changes were typical of rheumatoid arthritis.

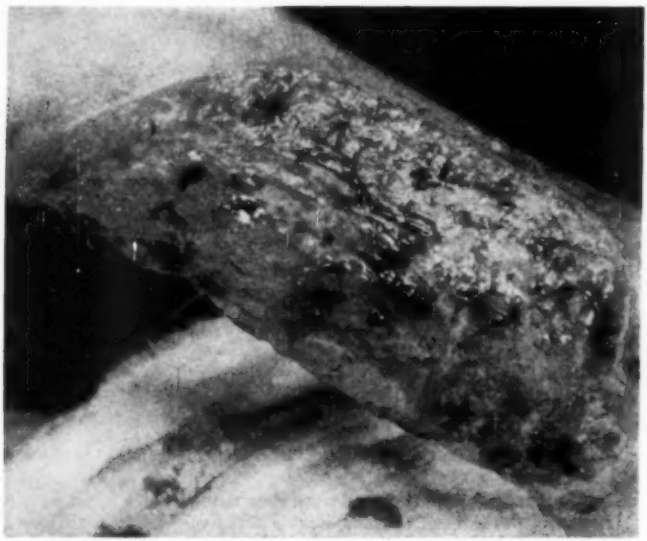

FIG. 4. *Case 2.* Area of extensive ulceration of leg which failed to heal before splenectomy.

Course. Zinc peroxide dressings were placed on the leg ulcer, and the patient was given multiple transfusions. Following the third transfusion, the hemoglobin rose to 7.9 gm. (50 per cent), red blood count was 2,250,000, and white blood count 3,500. The differential at this time was: 6 per cent myelocytes, 7 juveniles, 38 stabs, 15 segmented neutrophiles, 32 lymphocytes, and 2 monocytes. A sternal marrow biopsy showed slight hyperplasia and an increase in plasma cells. Proliferation of cells of the reticulo-endothelial system was suggested.

Exploratory laparotomy, with biopsy of the enlarged liver and spleen, was next performed. On microscopic examination, the liver showed an increase of glycogen

deposition but was otherwise not unusual. The spleen showed slight fibrous thickening of the capsule, some dilatation of the sinusoids, evidence of extramedullary hematopoiesis, increase in plasma cells, and increase in cells of the myeloid series. The endothelial lining cells of the sinusoids were not overly prominent, and there was no increase in connective tissue.

Additional transfusions were given, and the patient was prepared for splenectomy which was performed on May 15, 1945, the thirty-third hospital day. At operation, a 1,300 gm. spleen was successfully removed. There was no evidence of thrombosis or constriction of splenic vein, and specimens of blood obtained from the artery and splenic vein gave the following determinations:

Blood from Artery		*Blood from Vein*	
Hemoglobin 10.7 gm., 68%		Hemoglobin 11.6 gm., 74%	
Red cell count 3,591,000		Red cell count 3,857,000	
White cell count 2,050		White cell count 1,900	
Differential:		Differential:	
Myelocytes	6%	Myelocytes	4%
Juveniles	0%	Juveniles	2%
Stabs	14%	Stabs	18%
Segmented neutrophiles	20%	Segmented neutrophiles	6%
Lymphocytes	60%	Lymphocytes	68%
Monocytes	0%	Monocytes	2%
Platelets 300,000		Platelets 420,000	

The spleen contained a small hemangioma and a lymphangioma. Microscopic examination showed no phagocytosis of the white cells, but did show changes similar to those observed in the biopsy tissue. The findings were thought to be consistent with those of rheumatoid arthritis and infection, and contrary to the dubious attitude held by the Staff concerning the ultimate benefit of such a surgical procedure, the response was remarkable. On the first postoperative day the patient had a temperature elevation to 101.0° F., which dropped to 100.4° F. the second day, and thereafter was normal. White blood count on the first postoperative day was 2,450, with 2 per cent eosinophiles, 1 per cent juveniles, 34 per cent stabs, and 29 per cent lymphocytes. Platelet count was 390,000; prothrombin content was normal. On the second day the white count was 10,500, with 1 per cent myelocytes, 3 per cent juveniles, 20 per cent stabs, 73 per cent segmented neutrophiles, and 3 per cent lymphocytes. The white count gradually decreased, while the prothrombin content of the blood increased. Twenty-eight days postoperative the white count was 5,100, with 1 per cent juveniles, 1 stab, 57 segmented neutrophiles, 37 lymphocytes, 2 monocytes, and 2 eosinophiles. The basal metabolism rate was still abnormal, remaining plus 80. The leg ulcer showed marked improvement, clean granulations now appeared, and a split graft applied to the leg ulcer was approximately 70 per cent successful. The right lobe of the thyroid was resected on June 26, 1945, and microscopic examination of the tissue revealed a benign fetal adenoma. Three days postoperative the basal metabolism rate was plus 72. The patient was discharged on the eighty-first hospital day.

A clinic visit four months later showed a weight gain of 14 pounds and complete healing of the leg ulcer and all operative wounds. The patient displayed a healthy, flushed appearance of the skin and mucous membranes. A count at that time revealed a hemoglobin of 15.5 gm. (99 per cent), red blood cells 4,868,000; white blood cells 3,350; 7 per cent stabs; 32 per cent segmented neutrophiles; 59 per cent lymphocytes, and 2 per cent monocytes.

Five months later the patient was readmitted to the hospital for study. The leg ulcer was still well healed and showed no tendency toward degeneration. There had been a further weight gain of five pounds. Urinalysis showed a trace of albumin and a specific gravity of 1.020; there were a few red cells and occasional granular casts in the sediment. Hemoglobin was 15.4 gm. (98 per cent); red cell count, 5,060,000; white cell count, 3,400; stabs, 16; segmented neutrophiles, 32; lymphocytes, 40; monocytes, 4; and eosinophiles, 8 per cent. Hematocrit was 48 per cent; prothrombin content, 93 per cent of normal; platelet count, 230,000; icteric index, 4; nonprotein nitrogen, 20 mg. per cent; cephalin cholesterol flocculation, 4 plus; bleeding time, 2 minutes; clotting time, 2¼ minutes; and fragility test was normal. Basal metabolism had dropped to plus 28.

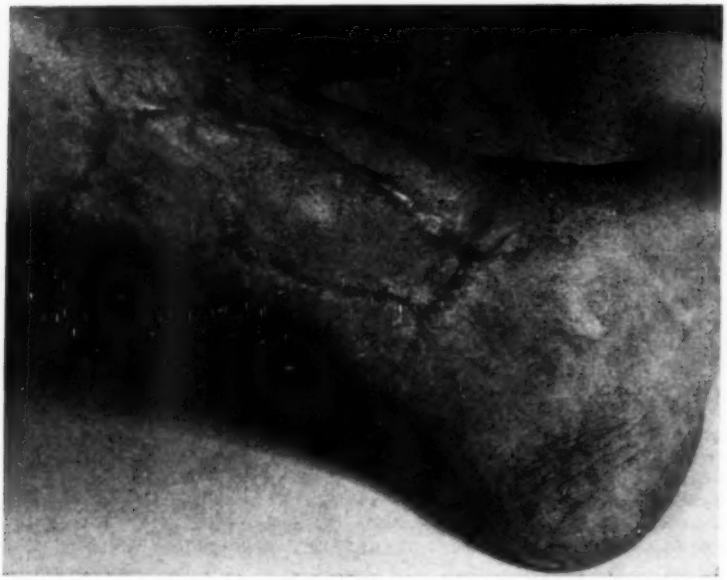

FIG. 5. *Case 2.* Complete healing of the area of ulceration 22 months after splenectomy.

This patient was last seen on March 12, 1947, 22 months after splenectomy. She was in excellent general condition. Her arthritis remained stationary, the leg was well healed (figure 5), and bleeding time, clotting time, and icteric index were normal. The platelet count was 200,000, and the complete blood count was as follows: Hemoglobin 16.8 gm., 116 per cent; red blood cells 5,640,000; white blood cells 12,900; stabs 8, segmented neutrophiles 29, lymphocytes 53, monocytes 8, eosinophiles 1, and basophiles 1 per cent.

DISCUSSION

In each case following splenectomy there were several significant changes for the better. Over a short period of time there was a gain of weight (14 pounds and 45 pounds), appreciable improvement in the general condition, and an increase in physical activity. In each case the red cell count and hemoglobin

returned to normal. In the white blood cell picture, a temporary alteration to a normal level gradually gave way to the previous leukopenic-neutropenic state. There was a diminution in the basal metabolism rate. Most encouraging was the initial improvement in the leg ulcers. Previous to splenectomy, meticulous local cleanliness and débridement had caused no improvement in the ulcers; following operation, healthy granulations appeared, and complete epithelialization was accomplished by skin grafting. Unfortunately, in the first case the ulcer recurred with the shedding of a small bone sequestrum; in all respects the lesion assumed its former appearance; the patient failed rapidly, and finally died. Leukopenia and granulocytopenia were present and clinical signs before death suggested a bleeding tendency. In the second case the ulcer has remained epithelialized and the patient is in excellent health. Leukopenia and granulocytopenia similar to the admission state are present, but the red blood cell series have persisted within normal limits since splenectomy.

These two cases do not present the common etiologic conditions causing chronic leg ulceration. There was no evidence that the ulcers were primarily infectious and vascular changes were at a minimum. In particular, syphilis and tuberculosis were excluded, and neoplastic disease was eliminated immediately by biopsy.

These two cases presented unmistakable joint alterations typical of rheumatoid arthritis. The arthritis was far advanced and quiescent, and there was no complaint referable to the joints other than loss of function due to ankylosis. There was no change in the condition of the joints following splenectomy. The basal metabolic rate in rheumatoid arthritis is usually normal and is more often subnormal than elevated,[1, 2] but both of our cases had basal metabolic rates elevated to values rarely encountered in rheumatoid arthritis. Although to our knowledge chronic leg ulcers of uncertain etiology have not been encountered in rheumatoid arthritis, Steinbrocker and Samuels,[3] in a careful study of the peripheral vascular status in rheumatoid arthritis, found vasomotor abnormalities in 65.9 per cent. These abnormalities were usually reflected in a reduction of arterial circulation. The authors did not record significant skin changes other than those usually associated with rheumatoid arthritis, and no case of leg ulceration was mentioned. Vascular alterations in our two cases were certainly no greater than those observed by Steinbrocker and Samuels, yet ulceration was present in each. Certainly an etiology other than vascular was suggested in these two cases.

Splenomegaly is found in 10 to 20 per cent of all cases of rheumatoid arthritis.[1, 4] Mild leukopenia with a relative lymphocytosis is not uncommon,[5] and liver dysfunction is found in 50 to 60 per cent of cases of severe rheumatoid arthritis.[2] Lymphadenopathy is present in 40 to 60 per cent and hypochromic anemia and weight loss are common.[5, 6] In 1924, Felty [7] reported several of these abnormalities occurring simultaneously in five cases, all of middle age (45 to 65 years) and showing marked weight loss (40 to 64 pounds) in four patients. There was rheumatoid arthritis of four and one-half years' average duration, splenomegaly, lymph node enlargement (axillary, inguinal, and epitrochlear) in three cases, slight secondary anemia in four, and marked leukopenia (1,000 to 4,200). Additional characteristics consisted of marked joint symptoms with rather benign objective changes, a yellowish-brown skin pigmentation, and a low-grade fever (two patients).

Our cases had characteristics similar to Felty's syndrome. However, lymphadenopathy and skin pigmentation were not observed, and in Felty's original report and in subsequent reports, leg ulcers were not observed.

The bone marrow biopsy in Felty's syndrome has consistently shown a hyperplasia,[8, 9, 10, 11, 12] as was found in our cases. Steinberg [9] observed identical changes in the bone marrow of 12 cases of rheumatoid arthritis without the picture of Felty's syndrome. Examination of the spleen in Felty's syndrome, where possible, has shown dilated sinuses,[8, 10, 12, 13, 14, 15] increased numbers of plasma cells,[8, 10, 12, 14, 15] erythrophagia,[8, 12, 13, 14, 15] increased numbers of eosinophiles,[10, 15] hyperplasia of the lining cells of the sinusoids,[8, 14] increased red pulp,[8] and diffuse fibrosis and myeloid activity.[10] Our cases showed dilated sinusoids and an increase in plasma cells. The picture was thought to be consistent with a chronic infectious process, and this interpretation has been placed on the changes in the spleen in Felty's syndrome.[10]

Splenectomy has been performed in Felty's syndrome with varying results. Hanrahan and Miller [14] reported the first splenectomy in 1932 with a marked improvement in the arthritis, anemia, leukopenia, and thrombocytopenia up to four months. Craven,[15] in 1934, reported a transient beneficial effect on the arthritis and the leukopenia for eight months, a disappearance of abnormal skin pigmentation, and an improvement in liver function following splenectomy. In 1935 Fitz [16] reported that Hanrahan and Miller's case died 18 months after operation and Craven's case died of general inanition and terminal lobular pneumonia 14 months postoperatively. In 1942 Steinberg [9] reported an improvement in general health and leukopenia following splenectomy but with an evident tendency to reversion to the former state. More encouraging are the cases of Zimmer [11] and Hirschboeck.[12] Splenectomy performed in one of Zimmer's cases resulted in loss of joint pains and a reversion of the blood picture to normal for 19 months. Hirschboeck reports one case of improved joint function and a normal blood picture for five years following splenectomy. His second case demonstrated a leukocytosis and granulocytosis for six weeks, at which time the patient succumbed to a pylephlebitis. The immediate results in our cases were also good, and persistent benefit is expected in the second case. However, leukopenia recurred in both.

It is evident that many of the distinguishing features of these two cases are not unknown in rheumatoid arthritis and Felty's syndrome. All of Felty's original cases showed skin pigmentation, although subsequent investigators have not always included this feature in their diagnostic criteria. The basal metabolic rates in our cases are suggestive of some other process, and leg ulcers have not been reported in Felty's syndrome.

The introduction of the entity primary splenic neutropenia by Wiseman and Doan [17] in 1939 and the relating of this disease to congenital hemolytic jaundice and essential thrombocytopenic purpura were important steps forward in the understanding of splenic physiology and function. Wiseman and Doan [18, 19] have now reported six cases of this disease and five additional cases have been reported by other authors.[20, 21, 22, 23, 24] The syndrome is characterized by marked neutropenia and splenomegaly. Histologic identification rests on the demonstration of phagocytosis of granular leukocytes of the circulating blood by the reticuloendothelial cells of the spleen, according to Wiseman and Doan.[18] This phagocytosis is a reflection of an accelerated destruction of granulocytes in the

spleen. The cases reported by Muether et al.[22] and Rogers and Hall [23] did not show phagocytosis of the granulocytes but were in all other respects similar, and Wiseman and Doan have accepted the case of Muether. Supravital staining more clearly demonstrates the phagocytosis, and this technic was not employed in the cases of Muether and Rogers and Hall. Splenectomy is apparently permanently curative; this is substantiated in all reports. Bone marrow studies show hyperplasia of the myeloid elements (also of the red cell series if hemolytic anemia is pronounced).

As previously mentioned, the relationship of splenic neutropenia to hemolytic anemia and thrombocytopenia is emphasized by Wiseman and Doan. It is pointed out that in the latter two diseases excessive destruction of red cells and platelets occurs in the spleen, and identical changes in varying degrees may be seen in primary splenic neutropenia. Associated icterus and purpura may be symptoms and signs in splenic neutropenia. There is a favorable response of all elements to splenectomy. Doan and Wright [18] have recently reported a case of congenital splenic panhematopenia in which there was a hemolytic anemia, thrombocytopenia, and granulocytopenia attributed to excessive destruction of the respective blood elements in the spleen.

Witts [25] has reported two cases of chronic leg ulcers in association with essential thrombocytopenic purpura. In neither case was the spleen palpable. Both the ulcers and the thrombocytopenia responded to splenectomy in the first case, but removal of the spleen caused no improvement of the ulcers or the platelet count in the second case. In 1940, Leger and Orr [26] reported two cases of leg ulcer associated with congenital hemolytic jaundice. Both conditions responded to splenectomy in each case. Wiseman and Doan's third case of primary splenic neutropenia, reported in 1942, had a chronic ulceration of the leg which had failed to respond to any treatment but which healed promptly following splenectomy. In addition, this patient had a basal metabolism rate of plus 26, and intermittent swelling and tenderness of various joints. Joint symptoms were also a feature of the first case. In the case of congenital splenic panhematopenia reported by Doan and Wright, there were recurrent skin lesions. Following splenectomy there was a reversion of the blood picture to normal and no further skin disorder appeared.

Certainly neither of our cases could be classified as a hemolytic anemia or a thrombocytopenic purpura. The absence of phagocytosis of the granular leukocytes in the spleen, and the ultimate indifferent response of the peripheral blood leukocytes to splenectomy would militate against the diagnosis of primary splenic neutropenia. Each case does show, however, a marked improvement in the preexisting anemia after splenectomy, as well as a temporary leukocytosis.

Other conditions which merit brief consideration are Banti's syndrome, sickle-cell anemia, leukemia, agranulocytosis, and Gaucher's disease. In the two cases we have reported, there was splenomegaly, anemia, and leukopenia, but no evidence of gastrointestinal hemorrhage. At operation the splenic vessels demonstrated no abnormality and examination of the spleen showed no significant increase in connective tissue. Leg ulcers are common in sickle-cell anemia, but the other identifying features such as sickling of the red cells, jaundice, leukocytosis rather than leukopenia, are absent in our cases. The diagnostic alteration in the bone marrow and spleen and the other obvious clinical features of leukemia,

agranulocytosis, and Gaucher's disease are not present in our two cases. However, it is of some interest that Lockie et al.[8] made a provisional diagnosis of leukemia, later corrected, in their case of Felty's syndrome and also instituted roentgen therapy, as in our first case. Leg ulcers have been reported in myelogenous leukemia,[27] but this is extremely rare.

We have been unable to fit our cases into any previously described clinical pattern, although they are in some respects similar to many. We have been unable to identify pathologic features which are unique. On the other hand, the clinical response to splenectomy appeared clear. There was a marked improvement in the total blood picture, although leukopenia recurred in each instance. A normal erythrocyte picture has persisted. There was a marked improvement in the leg ulcers with eventual complete epithelialization, but this was only temporary in one case. Whether this change in the leg ulcers is a reflection of the improved blood picture or whether it is due to the removal of some noxious agent with the spleen cannot be stated. There was an improvement in the general physical condition, which has persisted. The basal metabolism rate has shown a decrease commensurate with the correction in anemia, but it still remains well above normal levels.

The question naturally arises whether this is a distinct clinical entity or a combination of two or more, arising in the same individual, and there is no certain answer. When Wiseman reviewed these two cases it was suggested by him that probably more than one factor was at work in both of these patients. He felt that part of the granulocytopenia was due to hypersplenism with excessive destruction of the blood elements. It was suggested that the longer the granulocytopenia and chronically infected leg ulceration existed, the more difficult a permanent cure becomes. Added to this is a possible permanent inhibitory effect on the bone marrow by an unknown agent secondary to hypersplenism. He then suggested that following splenectomy, an improvement in the blood picture and leg ulcers could be predicted (as had occurred when he reviewed the cases), but subsequently a fall in the leukocyte count—and even recurrence of the ulceration—might be expected because of the other factors tending to produce granulocytopenia in these cases; namely, rheumatoid arthritis and chronic infection of long standing. That destruction of granulocytes in the spleen may not be of great importance in our cases is suggested by the essentially identical white blood cell counts taken from the splenic artery and splenic vein at the time of splenectomy in each case. This finding is in accord with the failure to demonstrate phagocytosis in the spleen. Hirschboeck [12] was able to show a white cell count of 11,700 in splenic arterial blood as against a count of 2,600 in splenic venous blood in a case of Felty's syndrome subjected to splenectomy. However, he did not observe phagocytosis of granulocytes in the spleen and favored a combination of the theories of splenic inhibition of the bone marrow and splenic phagocytosis in explanation of the leukopenia of hypersplenism. Recently Doan and Wright [19] have reported a case of splenic panhematopenia secondary to Gaucher's disease. Other similar cases were cited and it was hypothesized that splenic panhematopenia may occur secondary to many other diseases in which there is an associated hypersplenism. Perhaps the splenomegaly of rheumatoid arthritis through excessive destruction of blood elements and/or bone marrow inhibition might lead to a pancytopenia.

SUMMARY

Two cases are reported which are characterized by rheumatoid arthritis, splenomegaly, chronic leg ulcer, leukopenia and neutropenia, anemia, and elevated basal metabolism rate. Splenectomy has been of persistent benefit in one case (22 months following splenectomy). These cases do not appear to allow classification among well-recognized syndromes.

Addendum. The patient was again seen April 7, 1948, 35 months after splenectomy. She had no complaints, was gaining weight and the grafted area remained healed. Blood count showed RBC 5,350,000, hemoglobin 15 gm. (100 per cent), WBC 7,750 with stabs 8 per cent, segmented neutrophiles 53 per cent, lymphocytes 34 per cent, monocytes 4 per cent, eosinophiles 1 per cent. Platelet count 220,000.

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A CASE OF CYSTIC FIBROSIS OF THE PANCREAS ASSOCIATED WITH CHRONIC PULMONARY DISEASE AND CIRRHOSIS OF THE LIVER*

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Introduction

Cystic fibrosis of the pancreas is a rare disease of infancy and childhood which usually has a fatal termination within the first two years of life. This case is unusual in that the age at death was 17 years.

Case Report

A 17 year old boy was admitted to the medical service of the Toronto General Hospital, February 19, 1946, because of increasing shortness of breath, and died on March 30, 1946. His father stated that he had never been a robust child, and that since shortly after birth he had had about five daily bowel movements which were bulky, pale, soft, and very foul smelling. At the age of 10 years he contracted measles, followed by pneumonia. This illness was of 13 weeks' duration and was treated at another hospital. Ever since the above illness there had been a slight unproductive cough and undue shortness of breath when playing games; clubbing of the fingers and toes was first noted then. After September 1945 the shortness of breath on effort increased and was accompanied by slight swelling of the legs.

On January 2, 1946, he was examined by a private physician who noted that he was undernourished, and found persistent medium râles over both lower lung fields, moderate enlargement of the liver and edema of the ankles. About two weeks prior to admission a nasal discharge and malaise developed followed by increase in cough, which became productive of mucopurulent sputum. He continued to attend school, however, until 10 days before admission, when he was forced to remain in bed be-

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cause of increasing dyspnea, even at rest, and the development of a sharp stabbing pain over both sides of the lower chest posteriorly.

On examination he appeared acutely ill, was moderately dyspneic propped up in bed, and slightly cyanosed. He appeared underdeveloped. He was coughing oc-

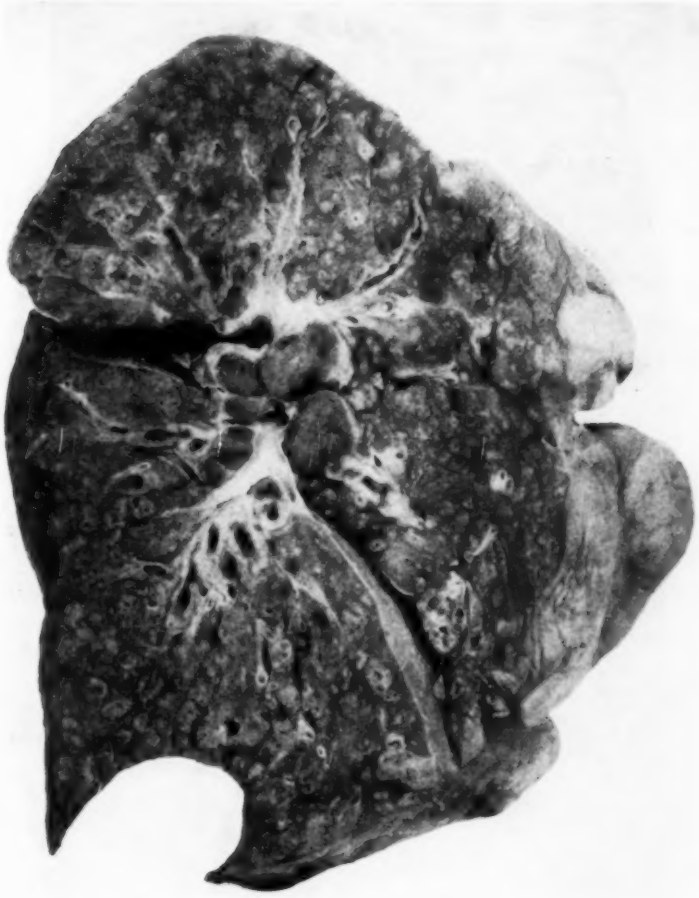

FIG. 1. Section of right lung showing scattered areas of consolidation, bronchiectasis, and enlarged peribronchial lymph nodes.

casionally and expectorating thick mucopurulent sputum. The rectal temperature was 103° F., the pulse rate was 110 per minute, and the respiratory rate 32. The jugular veins were not engorged. Blood pressure 110 mm. of mercury systolic and 50 mm. diastolic. The heart and trachea were in normal position. The chest was

barrel-shaped. Respiratory movement of the chest was reduced on both sides, more so over the left base. The lower borders of the lungs were one interspace lower than normal and there was loss of superficial cardiac dullness. The breath sounds were

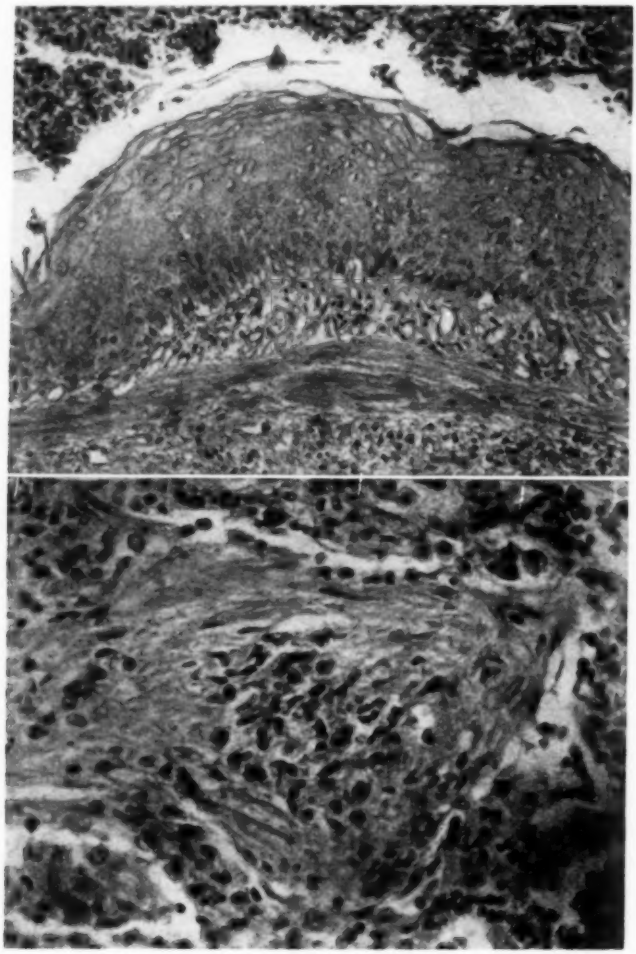

FIG. 2 (*Above*). Squamous metaplasia of bronchial epithelium. × 155.
FIG. 3 (*Below*). Organization of pneumonia exudate. × 335.

intense and vesicular in type. Numerous fine and medium râles were heard throughout both lung fields, especially at the bases. A friction rub was present over the lower chest posteriorly on both sides. The abdomen was distended and tympanitic. The liver was moderately enlarged; the surface felt smooth and firm. The spleen

was not palpable. There was no edema of the extremities. The fingers and toes were moderately clubbed. Neurological examination was negative except for absence of knee reflexes.

Urinalysis was negative. Hemoglobin 87 per cent; red cell count 4,700,000; white cell count 20,600, with a differential count of 94 per cent neutrophiles. The red cells were normal in size, shape, and hemoglobin content. The stools were bulky, pale, soft and very foul smelling and the total fat content was estimated to be 66 per cent of the dry weight. Serum calcium 8.2 mg. per cent; serum phosphorus 4.3 mg. per cent; alkaline serum phosphatase 47 units. Van den Bergh, negative direct, 0.4 unit. Serum proteins: total 7.8 gm. per cent composed of albumin 4.0 and globulin 3.6 gm.; fractionation at 13.5 per cent sodium sulfite 1.5 per cent; formol-gel 4+. Prothrombin time normal. Galactose tolerance test normal. Electrocardiogram showed sinus tachycardia. The sputum on culture grew many colonies of *Staphylococcus aureus hemolyticus*. Blood cultures were sterile. Chest roentgen-ray showed evidence of scattered areas of peribronchial infiltration throughout both lung fields. Roentgen-rays of the long bones revealed a moderate degree of diffuse osteoporosis, but no other abnormality.

FIG. 4. Inferior surface of liver showing gross lobulation.

The clinical diagnosis was acute bronchopneumonia, pulmonary emphysema, idiopathic steatorrhea and suspected portal cirrhosis.

The patient was placed in an oxygen tent in the orthopneic position. Penicillin, 15,000 units intramuscularly every three hours, was prescribed. A diet high in protein and carbohydrate and low in fat was ordered along with added vitamins A and D. There was an initial slight improvement and decrease in fever. However, after two weeks of this therapy a generalized urticarial reaction developed along with an increase in fever. Penicillin was therefore discontinued. The urticaria cleared quickly, but his general condition grew steadily worse; he became drowsy, took very little nourishment, and expectorated very little sputum, although the cough appeared to be productive. Urobilin was found in the urine in moderate amounts on several occasions, and he developed a slight anemia. There was a progressive fall of serum

albumin and rise of serum globulin, the values on March 26 being total 6.8 per cent, albumin 2.6 per cent, and globulin 4.2 per cent and fractionation at 13.5 per cent sodium sulfite was 1.6 per cent. The Van den Bergh and prothrombin time remained

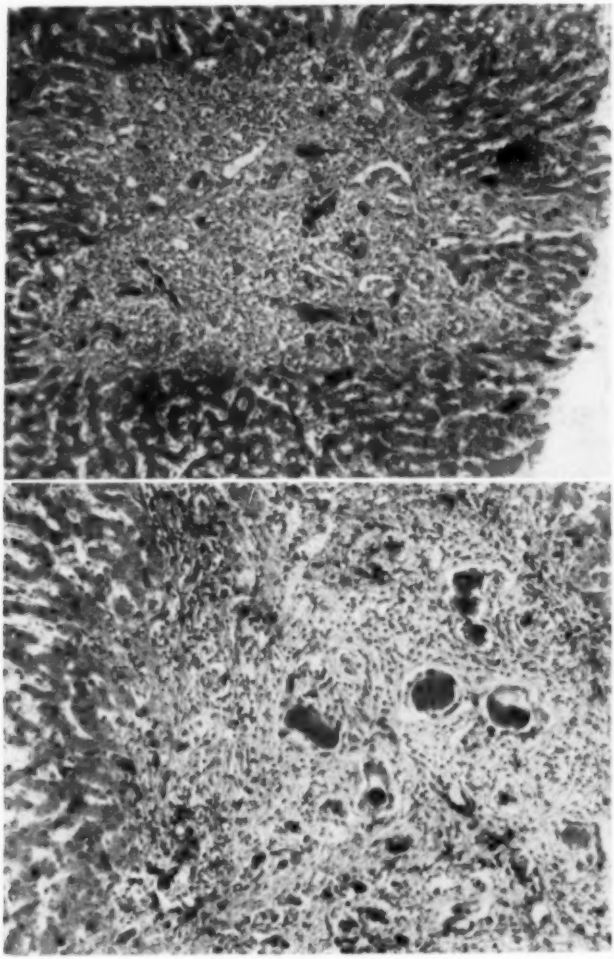

FIG. 5 (*Above*). Liver showing marked cirrhosis. ×92.
FIG. 6 (*Below*). Dilated bile ducts filled with inspissated material. ×110.

normal. Systemic penicillin therapy was again instituted on March 17 and continued until shortly before death, without benefit. He became stuporous, more cyanosed and dyspneic, and died on March 30.

Autopsy Findings: March 31, 1946 (14 hours after death).

The body was poorly nourished. Thick, greenish purulent material overflowed from the mouth. The ankles and wrists were unduly large and there was pitting edema of both lower extremities and moderate clubbing of the fingers.

Both pleural spaces were obliterated by fibrinous adhesions which were easily broken down. The lungs did not collapse when removed from the chest, but remained distended, as though fixed by inflation. The free margins were pale and feathery on palpation. Numerous diffusely scattered small nodules were felt throughout all lobes. On the cut surface these nodules were found to be grayish-red, circumscribed, consolidated areas surrounding the smaller bronchi, many of which were broken down to form tiny abscesses (figure 1). The bronchi throughout both lungs were dilated in a fusiform manner. The trachea and the whole of the bronchial tree were filled with thick, tenacious, greenish purulent exudate which clung to the mucosa. On culture it grew *Staphylococcus aureus* and *Streptococcus hemolyticus*. The bronchial mucosa had a granular, opaque and congested appearance. Numerous discrete, mod-

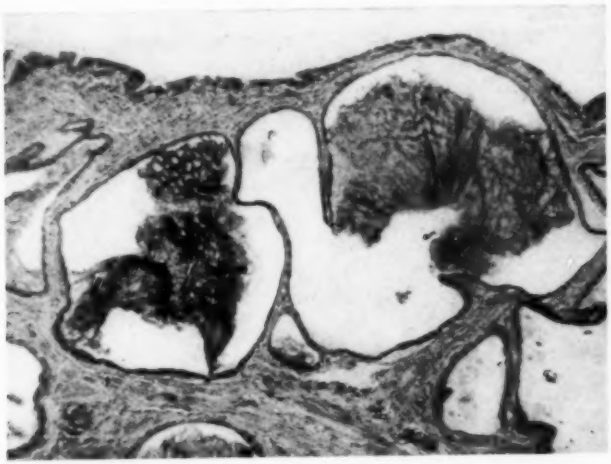

FIG. 7. Gall-bladder showing cyst formation. × 170.

erately enlarged tracheal and hilar lymph nodes were found. The most striking microscopic finding was that of extensive, patchy squamous metaplasia of the bronchial epithelium (figure 2). The mucous glands of the large bronchi were distended with mucus. There was extensive bronchiectasis in both lungs, the bronchi being filled with mucopurulent exudate and surrounded by patchy areas of bronchopneumonia, many of which showed early organization. The acute inflammatory process extended into the bronchial walls and in many of these complete breakdown had resulted in communication with small parenchymal abscesses lined by granulation tissue. There were numerous scattered discrete patches of organized alveolar exudate lying in relatively normal lung fields (figure 3). In some areas dilated air sacs typical of emphysema were seen. In other fields the picture was that of pulmonary edema. The visceral pleura was thickened by edema and extremely congested. In some areas the mesothelium was replaced by a fibrinopurulent exudate. The bronchial lymph nodes showed chronic lymphadenitis.

The liver weighed 1,475 grams, was grossly nodular and projected slightly beneath the right costal margin. The largest nodules were on the inferior surface, where they measured up to 4 cm. in diameter (figure 4). The cut surface was of a pale brown color, with a fine fibrous network running throughout the parenchyma. On microscopic examination the portal areas showed extensive irregular fibrosis,

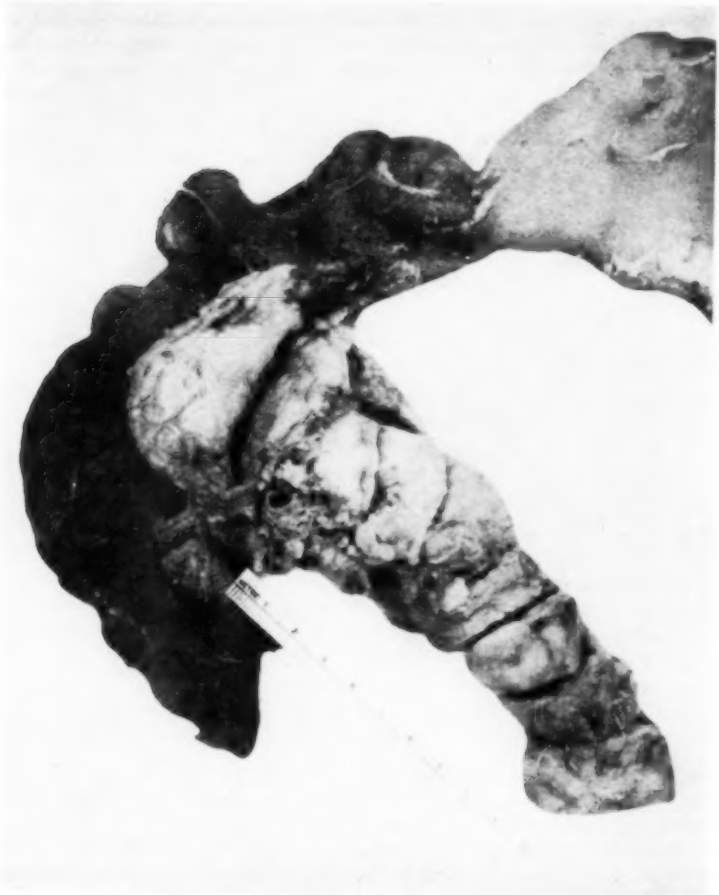

FIG. 8. Pancreas showing replacement of parenchyma by fat.

with proliferation of small bile ducts and slight infiltration by lymphocytes, plasma cells and histiocytes (figure 5). The fine strands of fibrous tissue extended in from the portal areas between the liver cords. In some fields there seemed to be an actual disappearance of parenchyma, with condensation of adjacent portal areas. This was also suggested by the reticulum-stained sections. There were numerous dilated bile

ducts in the portal areas, which were filled with either yellowish bile plugs or masses of eosinophilic, inspissated material (figure 6). There was no real evidence of regeneration of liver tissue. Moderate fatty metamorphosis was present, most marked in the central vein areas. The fat was stained orange with Sudan III.

The gall-bladder was almost empty and was the size of a normal appendix. The lumen contained four small, pale yellow, facetted stones which were embedded in mucus. The wall was thickened. The mucosa of the gall-bladder was a mass of dilated cystic spaces lined by flattened cells and filled with mucus (figure 7). The lining epithelium was remarkably well preserved, probably owing to the complete absence of bile in the lumen. There was no evidence of inflammation. The cystic duct was completely occluded by a stone immediately above the junction with the common bile duct. The common bile duct and the ampulla of Vater were patent.

The wall of the small intestine was thickened and edematous throughout, but more particularly so in the terminal ileum. The large bowel was similarly thickened in the cecum and sigmoid colon, and contained pale yellowish, pasty feces. Microscopic sections from the ileum and colon showed marked thickening of submucosa by edema. Numerous enlarged lymph nodes, similar to the tracheo-bronchial ones, were scattered throughout the mesentery and the region of the pancreas and porta hepatis.

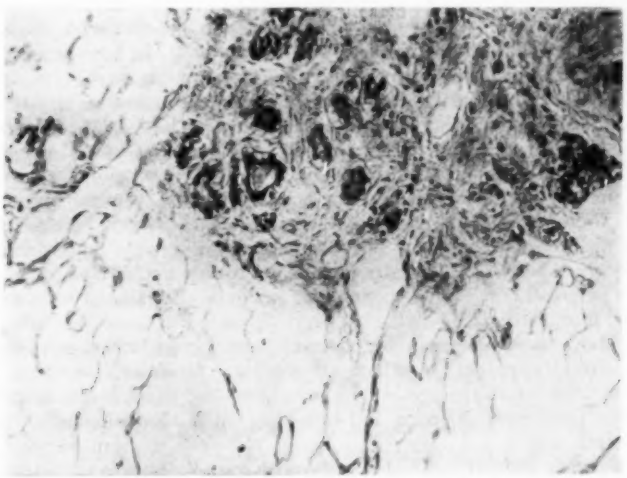

FIG. 9. Remnants of pancreatic tissue surrounded by fat. × 148.

The pancreas was of normal or slightly smaller than normal size (figure 8). The cut surface was pale and gelatinous. There was a marked decrease of the usual lobulation. A tiny duct was found which was too narrow to admit an ordinary probe. No communication with the duodenum could be proved and no accessory duct could be found. Numerous sections through the head, body and tail were examined and all showed profound fatty replacement of the acinar elements of the gland. Some sections across the entire width of the gland showed no recognizable acinar tissue. The islets of Langerhans were left as scattered foci of round cells embedded in the fat. There were, however, a few isolated irregular lobules of fairly dense fibrous tissue in which atrophic acini and small ducts could be identified, some of which were slightly dilated (figure 9). There was no evidence of active or chronic inflammation apart from an

occasional lymphocyte. A section stained with mucicarmine showed scattered masses of mucin, both intracellular and within the lumen.

No significant pathological change could be found on examination of the heart, stomach, duodenum, kidneys, spleen, and adrenals. There was no evidence of squamous metaplasia of the epithelium of the renal pelvis which might suggest vitamin A deficiency.

Discussion

Cystic fibrosis of the pancreas is a disease of infancy and childhood. It is usually manifest clinically by the celiac syndrome accompanied by chronic pulmonary disease, such as bronchiectasis or lung abscess, and a terminal bronchopneumonia.[1, 2, 3, 4] The gastrointestinal symptoms usually appear shortly after birth and consist of passage of large, loose stools, which are often recognized as fatty, distention of the abdomen and intolerance to fat in the diet; under-development follows. Infants living longer than a few weeks develop infection of the respiratory tract.[1, 2, 5, 7] On pathological examination, the pancreas is usually firmer, smaller and thinner than normal. The cut surface shows irregular lobulation with wide bands of connective tissue. Occasionally, however, the pancreas is grossly fatty.[1, 3, 6] Microscopically, the essential lesion is a profound disappearance of acini, replacement fibrosis and variable dilatation of small and large ducts which are filled with inspissated secretion. The term, cystic fibrosis of the pancreas, is derived from these microscopic findings. The islets of Langerhans are not affected. Lesions of the lungs are almost invariably present except in those infants dying during the first week of life.[1, 2, 3, 7] Infants living only a few weeks are found to have bronchopneumonia. Cases of longer duration commonly develop bronchiectasis or abscesses in relation to the smaller bronchi, interstitial fibrosis, pulmonary emphysema and terminal bronchopneumonia. Microscopically, a striking feature in some cases is squamous metaplasia of the bronchial mucosa. The invading organism in the lung is usually the *Staphylococcus aureus*.[1, 7] A fatty liver is a frequent finding and, uncommonly cirrhosis is present.[1, 2, 3] In Anderson's[1] series of 49 cases, 19 showed fatty livers and four cirrhosis.

The above syndrome may be confused with idiopathic celiac disease, the gastrointestinal symptoms of which are similar. However, the latter disease rarely develops before the age of nine months to two years, is not accompanied by chronic pulmonary infection and is seldom fatal. Pathologically, there are no pancreatic lesions.

This patient showed most of the above described features of cystic fibrosis of the pancreas. Steatorrhea had probably been present since shortly after birth. He was underdeveloped and had the pulmonary changes described above. The infecting organisms in the lung were the *Streptococcus hemolyticus* and *Staphylococcus aureus*, the latter being the most frequent invading organism in this disease. The pancreas showed a striking degree of atrophy of the exocrine parenchyma which is a constant finding in this syndrome.[2] The almost complete fatty replacement of the acinar elements with only slight fibrosis, is an occasional finding.[1, 6] It occurred in four of the series of 49 cases reported by Anderson. Microscopic evidence of cystic dilatation of the pancreatic ducts was only slight in our case. There was fatty infiltration and cirrhosis of the liver.

The etiology and pathogenesis of this disease are not known. The fact that the lesions in the pancreas have been found at birth strongly indicates a con-

genital defect in that organ.[1, 2, 3] Partial obstruction of the pancreatic ducts by inspissated secretion may lead to dilatation and atrophy of the ducts and acini, followed by replacement fibrosis. The subsequent development of chronic suppuration in the lungs has not been satisfactorily explained. Anderson [1] suggested that vitamin A deficiency, as a result of defective absorption of this fat soluble vitamin, leads to the squamous metaplasia found in various organs, including the bronchi. Metaplasia of bronchial epithelium with loss of cilia must hinder drainage of lung secretions, thereby predisposing to lung infection. However, lung infection is not common in adult humans or animals with pancreatic duct obstruction.[3] Farber has advanced the theory that body secretions generally are too viscid in this disease and that, in the bronchi and bronchioles, tenacious secretion may lead to a partial obstruction rendering them prone to infection.

The fatty infiltration of the liver is probably the result of the loss of the exocrine pancreatic function. Allan et al.[8] and Fisher [9] have shown that depancreatized dogs developed marked fatty infiltration of the liver, even though they were adequately treated with insulin. Moreover, Ralli et al.[10] and Montgomery et al.[11] produced fatty changes in the livers of dogs, following pancreatic duct ligation, which were indistinguishable from those of depancreatized dogs. A complete explanation for the deposition of fat in the liver under the above experimental conditions cannot be offered at present. But, it has been demonstrated, in the above animals, that the addition of raw pancreas to the diet prevented the abnormal deposition of lipids in the liver.[8, 9, 11] Similarly, Hershey [12] has shown that the oral administration of lecithin has the same effect, and Best et al.[13] have proved that choline, a component of lecithin, is likewise effective. It is possible that the lack of pancreatic juice interferes with the absorption of some dietary constituent which inhibits the deposition of abnormal amounts of fat in the liver.

The cirrhosis of the liver may be the result of prolonged fatty infiltration. Himsworth and Glynn [14] state that in animal experiments, a prolonged heavy fatty infiltration of the liver is an essential precursor and concomitant of diffuse fibrosis. Moreover, Chaikoff et al.[15] in a study of 16 depancreatized dogs maintained on insulin and an adequate diet for periods longer than one year, observed fatty livers in all of the animals, extensive cirrhosis in four, and abnormal fibrosis in another four. The duration of survival in patients dying with cystic fibrosis of the pancreas appears to be an important factor in the development of fatty infiltration and cirrhosis of the liver. In Anderson's [1] series a fatty liver was more frequently met with in children over six months of age and the cases showing cirrhosis varied in age from 17 months to 10 years.

Summary

A case of cystic fibrosis of the pancreas in a 17 year old male is presented. The outstanding features are: (*a*) symptoms suggesting steatorrhea since shortly after birth, (*b*) underdevelopment, (*c*) chronic pulmonary suppuration with squamous metaplasia of the bronchial epithelium, (*d*) cirrhosis of the liver, and (*e*) the almost complete replacement of acinar elements of the pancreas by fat and fibrous tissue.

A brief review of the literature of this syndrome is described and the etiology and pathogenesis of the lesions are discussed.

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PARALYSIS DUE TO REDUCED SERUM POTASSIUM CONCENTRATION DURING TREATMENT OF DIABETIC ACIDOSIS: REPORT OF CASE TREATED WITH 33 GRAMS OF POTASSIUM CHLORIDE INTRAVENOUSLY *

By F. Irby Stephens, M.D.,† *Asheville, N. C.*

Shortly after the discovery of insulin, Harrop and Benedict observed that insulin administration is followed by a decrease in the concentration of potassium in the serum.[1] Though it had been anticipated by several investigators, 23 years elapsed before Holler reported a case illustrating the possible serious consequences of this relationship in the treatment of diabetic acidosis.[2] Holler noted the development of profound weakness and eventual paralysis of the

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muscles of respiration in the course of treatment of a patient with diabetic acidosis, and demonstrated that this complication was associated with low serum potassium concentration. The administration of potassium salts resulted in dramatic improvement. Holler pointed out certain physiological mechanisms which might have induced the deficiency of serum potassium, and emphasized features which he considered responsible for the severity of the reduction of serum potassium in his patient, namely, the prolonged period of acidosis, the striking diuresis occurring during the period of treatment, and the large doses of glucose and insulin employed.

Nicholson and Branning [3] reported two similar cases, one of whom recovered following the administration of potassium chloride by mouth. Frenckel, Groen, and Willebrands recently described an additional case with recovery following treatment with potassium chloride orally.[4]

In the past year symptoms due to potassium deficiency have been recognized in two cases of diabetic acidosis in this hospital. One of these succumbed, it is believed, as a result of this complication. The other patient is reported in detail below. A feature of this case is the fact that a much larger quantity of potassium salt was administered than has been employed previously, a quantity which we believe more nearly approximates the actual deficiency present.

Case Report

A 28 year old married white female was admitted to the Johns Hopkins Hospital at 5:30 a.m., July 21, 1947 in diabetic acidosis. Diabetes had been discovered in May, 1943, when the patient had been admitted to another hospital in coma. The patient repeatedly failed to adhere to her diet or to take insulin regularly, with the result that in the ensuing four years she was admitted to this hospital on seven occasions for various complications of poorly controlled diabetes.

Seven weeks prior to the present admission the patient was discharged from another hospital apparently well controlled on a diet containing protein 100 grams, fat 70 grams and carbohydrate 175 grams, with 35 units of protamine zinc insulin daily. She is alleged to have adhered strictly to this regimen until seven days prior to admission, when she abandoned her diet and omitted insulin for a period of five days. Polyuria recurred, the patient became nauseated, and for at least 36 hours prior to admission vomited repeatedly. On the evening of the fifth day of insulin withdrawal the patient took 35 units of protamine zinc insulin and repeated this dose the following morning. Vomiting continued, the patient became increasingly drowsy, and she was admitted early in the morning of the seventh day in diabetic coma.

Rectal temperature was 97.6° F. The pulse was regular, 120 per minute, blood pressure was 120 mm. Hg systolic and 70 mm. diastolic and the respirations were 28 per minute, Kussmaul in type. The patient was semi-conscious. The breath had the odor of acetone. There was evidence of marked dehydration. The deep tendon reflexes were present though hypoactive throughout. There were no other significant findings on physical examination.

Urinalysis revealed strongly positive reactions for glucose, acetone and diacetic acid. Blood sugar was 560 milligrams per 100 c.c. and the carbon dioxide combining power of the serum was 6.3 milliequivalents per liter (14.0 volumes per cent).

The therapy and course during the first 27 hours in the hospital are presented in table 1. For purposes of discussion the course has been divided arbitrarily into four periods: (1) course prior to potassium therapy, (2) first period of potassium therapy, (3) second period of potassium therapy, (4) third period of potassium therapy.

Course Prior to Potassium Therapy: (5:30 a.m. to 2:25 p.m.) Crystalline zinc

TABLE I

Course and Details of Therapy During First 24 Hours

Time	Therapy		Blood Chemistry				Urine			Remarks
	Intravenous Fluids	Insulin units CZI	Sugar mg. %	CO_2 m.eq./L.	Serum K m.eq./L.	NPN mg. %	Glucose	Acetone	Diacetic Acid	
PERIOD I. COURSE PRIOR TO POTASSIUM ADMINISTRATION										
5:30 a.m.	200 c.c. 5% glucose; 100 c.c. saline		560	6.3			4+	3+	3+	Patient admitted in diabetic coma.
6:00	500 c.c. plasma	50					4+	3+	3+	
7:00		50					4+	3+	3+	
8:00	1,500 c.c. saline	50					4+	3+	3+	
9:00	750 c.c. M/6 Na lactate 200 c.c. 50% glucose	50	508	15.3		57	3+	3+	3+	
10:30		50					3+	3+	3+	Shallow respirations noted.
11:00										EKG evidence of low serum K. Figure 1A.
11:30	1,500 c.c. saline									
12:00 n	200 c.c. 50% glucose	50	800	13.2	1.8	42				
12:30 p.m.							3+	3+	3+	EKG changes more pronounced. Figure 1B.
1:30							3+	3+	3+	Gastric lavage.
2:00					1.4					EKG changes extreme. Figure 1C.
PERIOD II. FIRST PERIOD OF POTASSIUM THERAPY										
2:30 p.m.	500 c.c. 0.4% KCl and 0.6% NaCl									Complete flaccid quadriplegia.
3:00	500 c.c. 0.4% KCl and 0.6% NaCl									Definite improvement in EKG.
3:30	500 c.c. 0.4% KCl and 0.6% NaCl						3+	2+	1+	Marked improvement in EKG.
4:00	500 c.c. 0.4% KCl and 0.6% NaCl									Paralysis subsiding.

PERIOD III. SECOND PERIOD OF POTASSIUM THERAPY										
4:30 p.m.	1,000 c.c. 10% glucose	50	280	16.1	2.7		3+	1+	0	
5:00	1,000 c.c. 10% amigen						4+	1+	0	EKG evidence of further reduced serum K.
5:30	5 gm. KCl									Bigeminal rhythm.
6:00										Recurrence of flaccid quadriplegia.
6:30							4+	1+	0	
7:30					1.56		4+	1+	0	Progressively weaker.
9:00	500 c.c. saline									Gastric dilatation. 1,500 c.c. removed.
9:30										EKG indicates further reduction in serum K.
PERIOD IV. THIRD PERIOD OF POTASSIUM THERAPY										
10:00 p.m.	1,000 c.c. saline	25			2.1		3+	0	0	Immediate clinical improvement. EKG improved.
10:30	500 c.c. 2% KCl						3+	0	0	
11:30	1,500 c.c. saline 5 gm. KCl									
12:30 a.m. **		25					3+	0	0	Sustained improvement in muscular strength.
3:00 a.m. **	250 c.c. saline 500 c.c. 5% glucose 250 c.c. 2% KCl		368	23.3	2.2	49	1+	0	0	
6:00 a.m. **	I-V fluids discontinued	25								Sustained clinical improvement.
8:30 a.m.			152	16.1	2.4		1+	0	0	Able to sit up and eat.

For convenience, times are indicated to the closest half hour.

insulin was given hourly in doses of 50 units. Fluids were administered as a continuous intravenous infusion, as shown in table 1. The urine output during the period was 4,000 cubic centimeters. During this period 37 milliequivalents of potassium were excreted in the urine. She was given 650 cubic centimeters of water orally. A gastric lavage with 5 per cent sodium bicarbonate solution was performed. No gastric contents were obtained, and approximately 500 c.c. of the bicarbonate solution were left in the stomach. It is perhaps well to state that the above treatment is a considerable variation from the standard therapy of diabetic acidosis customarily employed in this clinic.

Four hours after admission it was noted that the patient's respirations had become rapid and shallow. The sensorium had cleared considerably, and the patient responded well. There was no dyspnea. The pulse rate was 120, and the blood pressure was 130/80. Ocular movements were performed normally, and there was no disturbance of speech or difficulty in chewing or swallowing. There was, however, marked weakness of the muscles of all four extremities and to a lesser extent of the neck muscles. Tendon reflexes were now absent throughout. There was no impairment of sensation.

The development of profound muscular weakness suggested the possibility of low potassium concentration in the serum. An electrocardiogram taken five hours after admission revealed sagging of the S–T segments and low amplitude of the T-waves in all leads (figure 1A). Serum potassium six hours after admission was 1.8 milliequivalents per liter. The electrocardiogram taken at this time showed further changes (figure 1B). Two hours later the potassium was further reduced to 1.4 milliequivalents per liter, and there were even more striking changes in the electrocardiogram (figure 1C). Meanwhile the patient became progressively weaker. Seven hours after admission muscle strength as measured by a dynamometer (Stoelting) was only nine kilograms in the right hand and eight kilograms in the left hand (normal, female, 20 to 30 kilograms). Thirty minutes later dynamometer readings were six kilograms in the right and five kilograms in the left hand.

First Period of Potassium Therapy: (2:25 p.m. to 4:20 p.m.) Nine hours after admission insulin and glucose were discontinued, and over the subsequent two hours the patient was given intravenously 2,000 cubic centimeters of a solution containing 0.4 per cent potassium chloride (54 milliequivalents of potassium per liter) and 0.6 per cent sodium chloride in distilled water. Two grams of potassium citrate were given orally during the first half hour. An electrocardiograph with a Sanborn cardioscope attachment was connected to the patient throughout the period of therapy. This permitted constant observation of the electrocardiographic changes and facilitated the taking of electrocardiograms at frequent intervals.

The potassium chloride solution was administered at a rate of 18 to 20 cubic centimeters per minute. Definite regression of the electrocardiographic abnormalities was observed within 10 minutes (figure 2A). Twenty-five minutes after beginning the infusion the patient had received 500 cubic centimeters of the solution (2.0 grams of potassium chloride or 27 milliequivalents of potassium) and further improvement was noted in the electrocardiogram (figure 2B). There was, however, no corresponding improvement in the clinical condition of the patient. In fact, she complained of numbness and tingling in both hands, and examination revealed a flaccid paralysis of both arms and legs. She was unable to raise or turn the head from side to side. Respirations were almost entirely diaphragmatic with hardly discernible excursions of the chest. There were, however, no complaints of dyspnea nor evidence of oxygen lack at any time. Speech, mastication, deglutition, ocular and facial movements were grossly unimpaired. The patient was able to move the toes of both feet only slightly. Deep tendon reflexes were unobtainable, and the plantar reflexes were absent. Sensation to pinprick and cotton wool was intact.

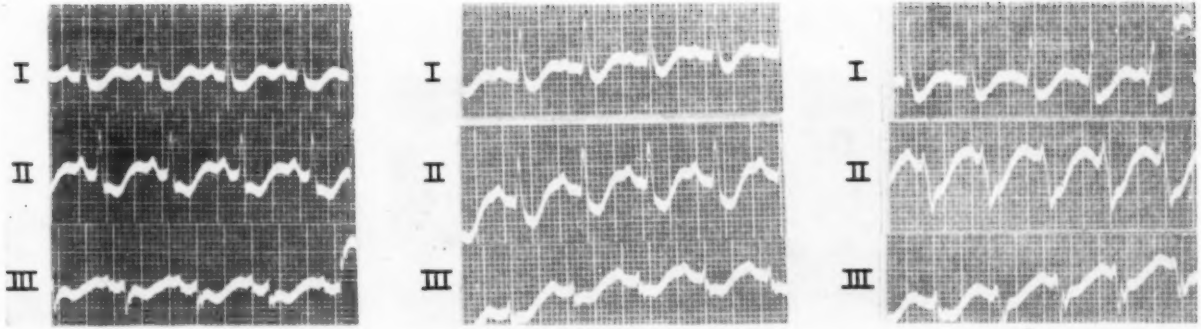


FIG. 1. Electrocardiograms prior to administration of potassium. Note depression and sagging of ST segments characteristic of low serum potassium. *A*. 11:00 a.m. Five and one-half hours after admission. Serum K at 11:55 a.m.: 1.8 m.eq. per L. *B*. 12:50 p.m. *C*. 2:15 p.m. Serum K at 2:10 p.m. 1.4 m.eq. per L.

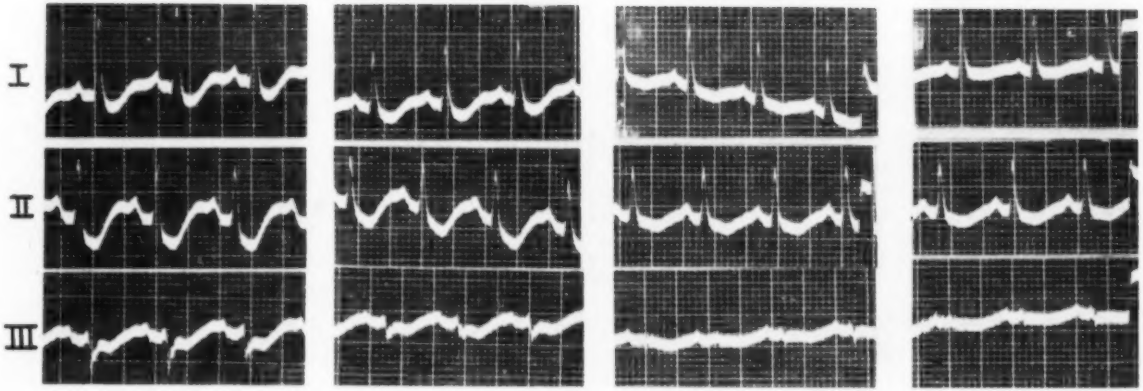


FIG. 2. Electrocardiograms during the first period of potassium therapy. Note gradual regression of changes of reduced serum potassium. *A*. 2:35 p.m. Ten minutes after beginning 0.4 per cent KCl intravenously. *B*. 2:50 p.m. After 2.0 gm. KCl intravenously and 2.0 gm. K citrate orally. *C*. 3:25 p.m. After 4.0 gm. KCl intravenously and 2.0 gm. K citrate orally. *D*. 3:55 p.m. After 6.0 gm. KCl intravenously and 2.0 gm. K citrate orally. Serum K at 4:20 p.m.: 2.7 m.eq. per L.

Potassium therapy was continued at approximately the same rate, and there occurred a gradual return of muscle power. Eight grams of potassium chloride were administered intravenously and 2.0 grams of potassium citrate were given by mouth during the two hour period, at the end of which the patient was remarkably improved. Respirations were deeper, and the arms and legs could be moved without difficulty. The paresthesias of the arms slowly subsided. Electrocardiograms showed gradual progress toward normal (figure 2C, D). At the end of the period the serum potassium concentration was 2.7 milliequivalents per liter. The blood sugar was 280 milligrams per cent, the serum carbon dioxide combining power was 16.1 milliequivalents per liter. Urinalysis showed a three plus qualitative test for glucose, a trace of acetone, and no diacetic acid. No glucose or insulin was given during this two hour period.

Second Period of Potassium Therapy: (4:20 p.m. to 9:40 p.m.) There was now begun an intravenous infusion of a mixture containing 2,000 cubic centimeters of water, 100 grams of Amigen, 100 grams of glucose and 5 grams of potassium chloride. This was administered at an average rate of 8 cubic centimeters per minute. The Amigen itself contained 4.5 milliequivalents of potassium. The 2,000 cubic centimeter solution, therefore, contained 5.33 grams of potassium chloride (72 millequivalents of potassium). Fifty units of crystalline zinc insulin were given subcutaneously at the beginning of this period.

Within 30 minutes an electrocardiogram showed return of the changes associated with a fall in serum potassium (figure 3A). Shortly after this, bigeminal rhythm was observed (figure 3B). The apical rate was approximately 120 per minute with a pulse deficit of 60 per minute. The ectopic beats could be abolished temporarily by pressure on the right carotid sinus but the arrhythmia immediately recurred (figure 3B). The patient became steadily weaker, and at the end of one and one-half hours again exhibited a complete flaccid quadriplegia. Three hours after beginning the Amigen-glucose-potassium mixture and the accompanying injection of insulin, the serum potassium had fallen to 1.56 milliequivalents per liter. The 2,000 c.c. glucose-Amigen-potassium chloride mixture was given over a period of four hours and 20 minutes at the conclusion of which the infusion was continued by the addition of 500 c.c. of 0.85 per cent sodium chloride solution. Gastric dilatation was recognized during this period and was relieved by the removal of 1,500 cubic centimeters of thick green fluid from the stomach. Following this the bigeminal rhythm disappeared and the electrocardiogram showed still more pronounced changes indicative of low serum potassium (figure 3C). The quadriplegia persisted.

Third Period of Potassium Therapy: (9:40 p.m. to 6:00 a.m.) In view of the recurrence of paralysis together with the evidence of further decrease in the level of serum potassium, potassium chloride was administered at a more rapid rate: 500 cubic centimeters of a 2 per cent solution of potassium chloride were added to 1,000 cubic centimeters of 0.85 per cent sodium chloride and given by continuous intravenous infusion. This solution containing 10 grams of potassium chloride (135 milliequivalents of potassium) was given over a period of two hours. Improvement in the electrocardiogram was apparent within 10 minutes (figure 4A). Within 30 minutes the patient was remarkably improved. She could once again move the extremities, though muscular weakness was evident and tendon reflexes were still absent. The serum potassium concentration 50 minutes after adding the potassium chloride solution was 2.1 milliequivalents per liter. At the termination of this infusion the patient was vastly improved and an electrocardiogram showed further change toward normal (figure 4B).

During the subsequent six and one-half hours an additional 10 grams of potassium chloride were administered intravenously, as shown in table 1. There was gradual improvement in muscle strength. No further changes of significance were noted in

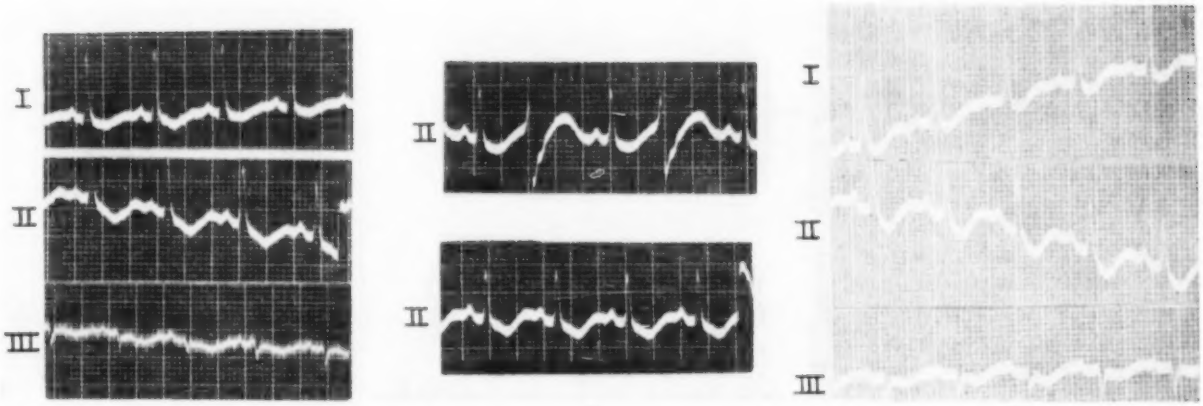


FIG. 3. Electrocardiograms during the second period of potassium therapy. Note reappearance of changes indicative of reduced serum potassium. *A*. 5:00 p.m. Thirty minutes after 50 units of insulin and beginning 10 per cent glucose-Amigen-potassium solution. *B*. 6:05 p.m. One and one-half hours after beginning the above therapy. Bigeminal rhythm has appeared (upper record) which reverts temporarily to normal rhythm following carotid sinus pressure (lower record). Lead II only. *C*. 9:25 p.m. Five hours after beginning above therapy at completion of 1000 c.c. 10 per cent glucose, 1,000 c.c. 10 per cent Amigen and 5.0 gm. KCl intravenously. Serum K at 8:30 p.m.: 1.6 m.eq. per L.

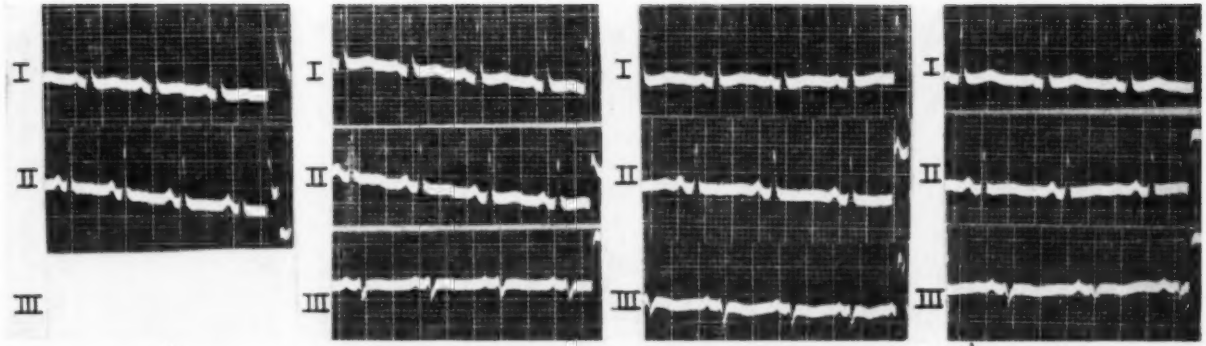


FIG. 4. Electrocardiograms during the third period of potassium therapy. Note the prompt regression of electrocardiographic changes of marked reduction of serum potassium concentration. *A*. 9:45 p.m. Five minutes after beginning 0.66 per cent KCl solution intravenously. *B*. 11:30 p.m. Following 10.0 gm. KCl intravenously in previous 1.8 hours. *C*. 2:30 a.m. Following 15.0 gm. KCl during previous five hours. Serum K at 3:00 a.m.: 2.2 m.eq. per L. *D*. 6:00 a.m. At conclusion of potassium therapy. Serum K at 8:00 a.m.: 2.4 m.eq. per L.

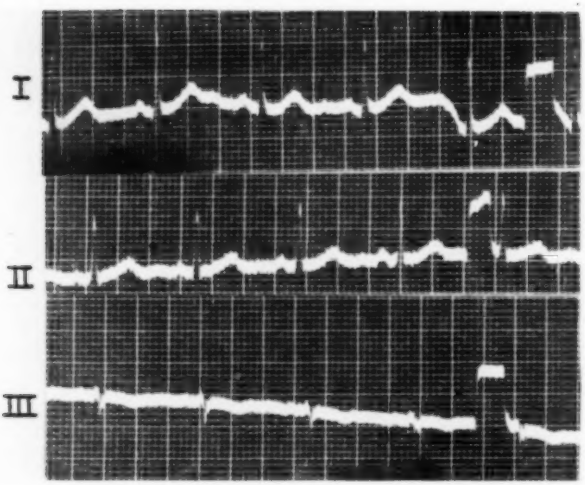


FIG. 5. Electrocardiogram on third hospital day. Normal electrocardiogram. Serum K at this time: 3.3 m.eq. per L.

the electrocardiograms (figure 4C, D). Intravenous therapy was discontinued 24 hours after admission at which time the patient was able to move about and feed herself without difficulty. Blood studies 27 hours after admission gave the following results: serum potassium 2.4 milliequivalents per liter, blood sugar 152 milligrams per cent, serum carbon dioxide combining power 16.1 milliequivalents per liter, serum chloride 109.5 milliequivalents per liter.

The remainder of the hospital course was without incident except for development of a mild urinary tract infection. The patient was able to take a full diet by mouth beginning at noon on the second day in the hospital. The daily potassium intake was calculated and the level of serum potassium determined each morning (table 2). It will be noted that the serum potassium did not reach normal levels until the fifth hospital day. An electrocardiogram on the third hospital day was normal (figure 5).

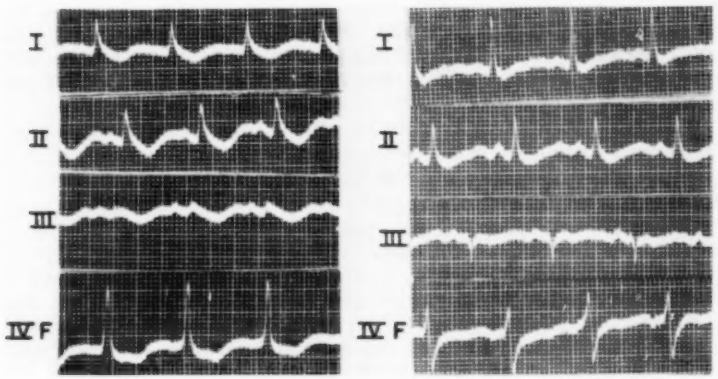
TABLE II

Serum Potassium Levels During Recovery from Diabetic Acidosis

Date	Daily Oral Intake of Potassium	Serum Potassium Level
7–23–47	3.1 gm. (79.0 m.eq.)	3.3 m.eq./L. (9:30 p.m.)
7–24–47	3.8 gm. (96.9 m.eq.)	3.3 m.eq./L. (8:30 a.m.)
7–25–47	3.7 gm. (94.3 m.eq.)	3.8 m.eq./L. (8:30 a.m.)
7–26–47	4.0 gm. (102.0 m.eq.)	3.95 m.eq./L. (8:30 a.m.)
7–27–47	Not calculated (diet unchanged)*	3.5 m.eq./L. (8:30 a.m.)
7–28–47	Not calculated (diet unchanged)*	4.1 m.eq./L. (8:30 a.m.)
7–29–47	Not calculated (diet unchanged)*	4.8 m.eq./L. (8:30 a.m.)
7–30–47	Not calculated (diet unchanged)*	3.8 m.eq./L. (8:30 a.m.)
7–31–47	Not calculated (diet unchanged)*	Not determined
8– 3–47	Not calculated (diet unchanged)*	4.6 m.eq./L. (8:30 a.m.)

* Throughout this period the patient was given a normal diet containing protein 100 gm., fat 70 gm., and carbohydrate 175 gm. Calculations were made by Miss Janette C. Carlsen, chief ward dietitian, Osler Medical Clinic. Calculations were based on actual food intake and standard tables (Sherman, H. C.: Chemistry of Food and Nutrition, 7th Edition, 1946, New York, Macmillan Company).

In the light of the events described above, the previous hospital admissions of this patient are of interest. The patient was admitted for diabetic acidosis on three occasions in 1944 and 1945. On two of these admissions the acidosis was treated by the method then customarily employed in this clinic, which consisted of accomplishing the initial hydration by the use of intravenous isotonic sodium chloride and sodium lactate solutions without administration of glucose until the blood sugar had fallen to moderate hyperglycemic levels. During the second admission in October, 1944, however, the patient was treated by a method similar to that employed during the present admission, i.e., by the immediate administration of glucose together with normal saline. Treatment during the first 12 hours consisted of 210 units of crystalline zinc insulin and a total of 7,500 cubic centimeters of fluid intravenously containing 150 grams of glucose.



A B

FIG. 6. Electrocardiograms during previous admission for diabetic acidosis. During this admission treatment consisted of large quantities of insulin and glucose. *A*. 24 hours after admission. *B*. 72 hours after admission.

Because of protracted vomiting, intravenous therapy was continued throughout the first two and one-half days in the hospital. The clinical course was satisfactory, but review of electrocardiograms taken on the second and fourth days of that admission indicate the presence of low serum potassium (figure 6A, B).

DISCUSSION

Paralysis associated with reduced serum potassium concentration is an uncommon but serious complication of therapy of diabetic acidosis.[2, 3, 4] Some reduction in serum potassium is frequently present during treatment of diabetic acidosis, but hypokalemia of the degree exhibited by this patient is rarely encountered.[5, 6] The neurologic manifestations, consisting of progressive muscular weakness and finally flaccid paralysis of the extremities, are similar to those seen in familial periodic paralysis.[7] The correlation between neuromuscular dysfunction and reduction in serum potassium concentration in these two conditions has been pointed out by previous writers.[2, 3, 4]

The syndrome is easily recognized. In the patient reported here the paralysis was limited to the musculature of the extremities and trunk, the cranial nerves being little affected. Breathing was extremely shallow and the respiratory rate

increased, but there was never any dyspnea, nor were there signs of oxygen lack. In the case reported by Holler, respiratory embarrassment was perhaps the outstanding feature. Nicholson and Branning described respiratory difficulties in two patients, one of whom also had difficulty in swallowing.

The physiological mechanisms responsible for the reduction in serum potassium concentration in these instances will be mentioned only briefly. The dehydration which characterizes diabetic acidosis results from the loss of both intracellular and extracellular water. Potassium is lost from the cells with water and is excreted in large quantities in the urine.[11] The concentration of potassium in the extracellular fluid, however, remains normal or may be slightly elevated. The administration of insulin produces a reduction in serum potassium concentration in both normal and diabetic individuals.[1] The administration of large amounts of glucose has a similar effect.[8] This reduction in serum potassium has been shown to be the result of movement of potassium from the extracellular fluid into the tissue cells in the company of glucose—a normal response to increased glycogen formation.[9, 10]

In diabetic acidosis, even after the institution of insulin and glucose therapy, some patients continue to excrete large quantities of potassium in the urine.[12] During the nine hour period prior to potassium therapy, our patient excreted 37 milliequivalents of potassium in the urine. This loss is sufficient to account for a marked reduction in the potassium content of the extracellular fluid if there were no more potassium added from other sources. Thus, if insulin retards the movement of potassium from the cells to the extracellular fluid, and potassium continues to be excreted in the urine, the potassium in the extracellular fluid may fall to dangerously low levels. More detailed studies will be required to describe with accuracy the electrolyte exchanges and renal mechanisms involved.

The administration of large amounts of glucose may be a factor in the production of hypokalemia. It is possible that the diuresis secondary to hyperglycemia in this situation produces an increased urinary excretion of potassium. It seems significant that four of the five instances of paralysis associated with low serum potassium occurred in patients treated with liberal amounts of glucose.

In order to avoid the dangerous complication seen in this patient, it is necessary to recognize early the development of hypokalemia and to institute therapy at once. The greatest fall in serum potassium occurs during the first 24 hours. Certain features common to the cases of paralysis thus far reported should, when encountered, lead one to anticipate this complication. These are: a history of poorly controlled diabetes, a prolonged period of acidosis precipitated by the withdrawal of insulin, the use of large quantities of glucose intravenously, and the excretion of a large volume of urine during treatment.

In situations where potassium determinations are not readily available, the electrocardiogram provides a convenient method for detecting the presence of low levels of serum potassium. The electrocardiographic changes in this patient were quite specific and sufficiently striking to enable clinicians to make the diagnosis of hypokalemia prior to its confirmation in the chemical laboratory. It should be noted that diagnostic alterations were seen only after there had been a fall in serum potassium to levels below 2.5 milli-equivalents per liter. Important from the point of view of therapy is the fact that the changes were recognizable well in advance of the development of paralysis and respiratory

difficulty. Repeated cardiographic observations were invaluable throughout the course in estimating the response to therapy.

The outstanding electrocardiographic changes are seen in the ST segment and T-waves. The earliest change noted is reduced amplitude in the T-waves. With more marked reduction in serum potassium there is striking sagging of the ST segments below the isoelectric lines. The changes observed in this case are similar to those reported by previous writers.[2, 15, 16, 17, 18] In the presence of organic heart disease, digitalis administration, or other complicating electrolyte abnormalities, the interpretation of the cardiographic changes may become more difficult.

A considerably greater amount of potassium was administered to this patient than was employed in the previously reported cases. Holler gave 5.5 grams of potassium chloride intravenously and 4 grams of potassium citrate by mouth. Nicholson and Branning's treatment consisted of 3.6 grams of potassium chloride orally. Frenckel and his associates obtained good results with 4 grams of potassium chloride by mouth. Our patient responded initially to 8.0 grams of potassium chloride by vein, but suffered a relapse following subsequent glucose and insulin therapy despite the addition of potassium chloride to the intravenous infusion.* A total of 33.3 grams of potassium chloride was administered in the course of 15.5 hours. Even this amount was not sufficient to raise the serum concentration to normal. During the period of potassium therapy, 73 milliequivalents of potassium (equivalent to less than six grams of potassium chloride) were lost in the urine and vomitus. Though the amount of potassium administered seems large, it is of the same order of magnitude as the deficit that has been shown to occur in some cases of diabetic acidosis.[11] In this case, potassium was given intravenously in solutions containing from 0.25 per cent KCl (36 milliequivalents per liter) to 0.66 per cent KCl (90 milliequivalents per liter), at rates varying from 1 gram to 8 grams of potassium chloride per hour.

In the cases reported thus far, the administration of potassium has been employed as an emergency measure to combat the serious effects of reduced serum potassium. It would appear reasonable to administer potassium salts early in the course of therapy of diabetic acidosis as a prophylactic measure. The administration of potassium salts is not without danger, however. Too rapid intravenous injection may result in abnormally high concentrations producing heart block and cardiac standstill.[10] The administration of potassium salts is especially hazardous when renal function is impaired and should never be employed until an adequate urine flow has been assured.[13, 14] Detailed studies are needed to outline the criteria and indications for the use of potassium salts prophylactically in diabetic acidosis.

Summary

1. A case of paralysis associated with reduced serum potassium concentration occurring during treatment of diabetic acidosis is reported.

2. The amount of potassium administered to this patient is considerably greater than amounts previously employed in this condition.

3. It is important to anticipate the development of hypokalemia and, when it occurs, to institute treatment promptly in order to avoid the serious effects of marked reduction in serum potassium levels.

* What effect, if any, the administration of protein hydrolysate may have exerted is not clear.

4. The electrocardiogram offers a rapid and convenient method for the detection of reduced serum potassium concentration and is valuable as a guide to therapy when potassium salts are employed.

The author is indebted to Dr. J. E. Howard for assistance in the preparation of this paper and for permission to use balance data on this patient.

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SPOROTRICHOSIS, A PROTEAN DISEASE: WITH REPORT OF A DISSEMINATED SUBCUTANEOUS GUMMATOUS CASE OF THE DISEASE *

By Edward P. Cawley, M.D., *Ann Arbor, Michigan*

Diseases for which there exists a specific therapeutic agent are not numerous. Sporotrichosis alone, of all the deep mycoses, belongs in this unique category, which implies that a positive diagnosis of such an infection is tantamount to a significant and worthwhile therapeutic accomplishment. Fewer than 200 cases of sporotrichosis, many of these not verified, had been recorded in this country by 1932.[1] Since that time, however, the proved incidence of the disease has mounted with such rapidity that it now constitutes a disease to be reckoned with on occasion by physicians in every branch of medicine.

Within the genus sporotrichum are several species, most of which are not of clinical significance. *S. schenkii* and *S. beurmanni* are those isolated with greatest frequency from human infections, the former being most prevalent as a cause of disease in America.[2] The organism grows well aerobically at room temperature on such a simple medium as Sabouraud's dextrose agar. Within seven to 10 days the colony is apparent as a white aerial growth which gradually becomes compact and convoluted resembling, according to one observer, worm casts in the sands of the seashore.[3] After a few weeks it is darkly pigmented. If material for inoculation is obtained from secondarily infected lesions there is sometimes an over growth of bacterial contaminants. Incorporation of 50 units of penicillin in the culture medium of each tube or Petri dish will, however, inhibit the growth of a majority of such contaminants, and not interfere materially with growth of the fungus. Culture mount demonstrates an abundance of fine mycelium with numerous short lateral branches supporting pyriform microconidia in such a manner that resemblance to the petals of a flower is often striking. Direct examination of material from which the organism can be cultured with facility seldom reveals the parasite. It is equally as difficult to discern in biopsy specimens although a method has been described which in the experience of the author [4] has proved a valuable aid in detection of the organism in pus and tissues.

Under most circumstances a fungus of low virulence, the sporothrix doubtless requires suitable soil for its röle as a pathogenic agent, the disease sporotrichosis probably developing in most instances because of a lessened resistance of the host at the time of inoculation.[5] The fungus is exceptionally hardy and is known to thrive in all parts of the world, often as a saprophyte on plants, flowers, grasses and vegetables. Its occurrence in the normal human pharynx and gastrointestinal tract has been adequately verified as has also its ability to permeate the intact intestinal mucosa. It is more than probable that in the latter situation the organism is carried through the intestinal wall by migratory phagocytes.[5] The inoculation by infected vegetable matter of a broken area of skin or mucous membrane is doubtless the mode of infection in most cases of human sporotrichosis, considerable attention having been devoted to the disease

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as an occupational dermatosis.[6] At least two investigators have been infected while working with cultures of the organism and it has been shown that individuals may acquire this mycosis subsequent to the handling of dressings from patients with the disease.[1] Less common sources of infection cited by various authors have been those reputedly acquired from horses and from the bite of a rat, gopher, white mouse, parrot and hen.[5] Some cases of sporotrichosis in France were believed to have occurred subsequent to various intradermal tests.[7] Of considerable interest is the observation that involution of pharyngeal lesions of sporotrichosis may be followed by continued presence of the organism as a saprophyte, rendering the patient a typical "carrier".[1] Occurrence of the disease following cutaneous inoculation of an abrasion by means of the saliva of such a "carrier" has been recorded.[5]

Clinical Aspects of the Disease Sporotrichosis

A previous observation [5] regarding the clinical polymorphism exhibited by sporotrichosis is an apt one, this feature occasionally being of diagnostic import, especially as regards lesions of the skin. Although the disease is usually divided, for purposes of description, into the cutaneous and systemic types, it is worthy of note that a preponderance of all cases demonstrate involvement of the integument to a variable degree and that demonstrable visceral lesions are most unusual.[8]

When the skin is involved the infection is practically always primary there.[1] The localized lymphangitic type, with a primary lesion at the site of inoculation about the hands or feet, not infrequently simulating a syphilitic chancre, is the variety seen most often in America. It is usually accompanied by an ascending, relatively indolent and painless lymphangitis and few or several gummatous lesions resembling the primary sore and arranged in linear fashion along the course of the involved lymphatics. Palpable regional adenopathy is infrequent and the disease most often remains localized to the involved extremity.

Multiple disseminated subcutaneous gummatous sporotrichosis is encountered frequently in France, though rarely in this country. It is characterized by the occurrence of small, firm, painless subcutaneous nodules, often widely distributed, the lesions softening in their central portion, with eventual production of a miniature life buoy-like structure if the contents are evacuated. These involute after a few weeks or months, only to be succeeded by further crops of similar lesions. On occasion this type of the disease is manifested by an agglomeration of polymorphous lesions which pose a difficult problem in diagnosis.

Systemic sporotrichosis may occur subsequent to dissemination of the disease from a primary cutaneous lesion or lesions, although more frequently it is not possible to demonstrate with certainty a primary focus. Involvement of conjunctival, nasal, lingual, pharyngeal, oral, laryngeal and intestinal mucous membranes has been noted. Gastrointestinal sporotrichosis, however, is exceedingly rare.[1] Osseous lesions are not infrequent and may simulate those of syphilis. Muscular, lymph node and articular involvement has been recorded on several occasions. Cerebrospinal sporotrichosis is for practical purposes a non-entity and the same is true of the pulmonary variety of the disease, one investigator having found only two cases in the entire literature where evidence of the latter type of involvement was at all convincing.[8] A most unusual example of sporotrichosis

accompanied by lesions of the skin, spleen, liver, kidneys, myocardium, adrenals, cerebral cortex and bone marrow has recently been recorded.[9]

Sporotrichosis of itself seldom evokes significant symptomatology. General health is not altered unless and until the process continues untreated for a long period of time, after which intervening infection may complicate the issue and eventuate in a fatal outcome. As with others of the deep mycoses, sporotrichosis has little if any tendency to spontaneous involution and may persist for years if the correct diagnosis is not made and appropriate therapeutic measures instituted.

Diagnosis

Although demonstration of the causative organism, usually by cultural methods as previously described, is a prime requisite for a positive diagnosis of sporotrichosis, the skin test may on occasion be helpful. The antigen, known as sporotrichin, is injected intracutaneously, the test being read after 48 hours. If it is negative, this mycosis can be eliminated from the realm of diagnostic possibilities. A positive reaction is of considerably less significance and may indicate presence of the disease in question, that the person under consideration is a so-called "carrier" or be merely a cross reaction produced by another mycosis. Animal inoculation is seldom a pre-requisite to the diagnosis of sporotrichosis although intraperitoneal injection of infected material produces a sporotrichotic orchitis in the white rat which may evolve even more rapidly than cultures of the organism. The histopathology of sporotrichosis is usually neither distinctive nor diagnostic, being granulomatous in character, and detection of the fungus in microscopic sections is not a frequent occurrence.

The differentiation of sporotrichosis from other diseases is usually accomplished with ease, but on occasion may tax the diagnostic acumen of the ablest physician. Syphilis and tuberculosis are probably simulated most often, although sporotrichosis occasionally mimics pyogenic infections and other lesions of mycotic origin, notably those of blastomycosis, actinomycosis, coccidioidomycosis and histoplasmosis. A protracted illness, which is accompanied by indolent cutaneous or subcutaneous gummatous lesions having a distribution suggestive of lymphatic dissemination but without the usual inflammatory signs of a coccal infection, and which has failed to respond to ordinary surgical procedures [5] warrants thorough investigation and study as to the possibility of the disease being sporotrichosis. The acknowledged rarity of visceral sporotrichosis is of considerable import in the differential diagnosis of abstruse internal lesions and is for reasons previously cited, of practical significance to the roentgenologist confronted with an obscure pulmonary lesion suspected of being mycotic in origin.[8]

Treatment

In contradistinction to others of the deep mycoses, cases of sporotrichosis respond almost without exception to prolonged and intensive therapy with the iodides. On rare occasions the disease progresses despite adequate treatment,[10] such examples usually being of the disseminated variety. Continuation of the medication for one month after no further evidence of the disease can be demonstrated is advisable in order to prevent recurrences. It seems worthy of note that

numerous individuals with sporotrichosis have doubtless been stigmatized, in the past, as having syphilis because of a therapeutic response to the iodides.[5] In addition to such medication, judicious roentgen therapy is often useful as a therapeutic adjunct, especially in treatment of the localized lymphangitic type.

Report of a Case of Multiple Disseminated Subcutaneous Gummatous Sporotrichosis

R. F., a white male, aged 70, was admitted to the Dermatology Service of the University of Michigan Hospital on October 9, 1946, because of an extensive cutaneous eruption of several weeks' duration. The patient had first noticed an ery-

Fig. 1. The widespread distribution of lesions is apparent in this photograph.

thematous, split-pea size papule on the lower back which softened and became ulcerated within a few days and was followed rather promptly by lesions which pursued a similar course on the right thigh and right temporal region. Approximately two weeks before admission numerous similar lesions appeared on widely scattered portions of the integument, including the face, neck, trunk and extremities. The only subjective manifestation was mild pruritus.

Before his retirement at the age of 60, the patient had been a lumber dealer and farmer. Within recent years, however, his contact with plants, shrubs and other vegetation had been minimal. During the summer preceding onset of the efflorescence he had eaten fresh vegetables in abundance, but all had been thoroughly cleaned, in-

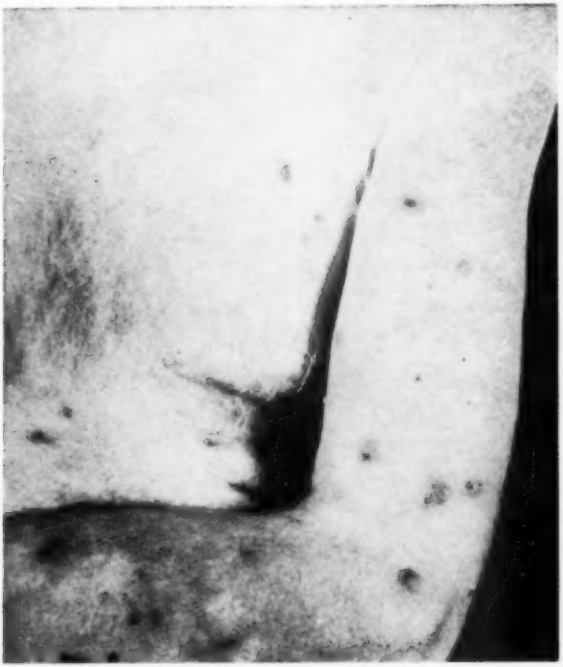


FIG. 2. Lesions on the left arm shown at close range. Several have ruptured leaving the typical central crater-like depression surrounded by an indurated ring.

sofar as he was aware. Roentgen therapy had been administered to a basal-cell carcinoma of the right cheek with satisfactory result, at the age of 62, and he had had a transurethral resection because of benign prostatic hypertrophy four years later. His past history otherwise was significant only in that he had been told on numerous occasions in the past, because of frequent respiratory infections, that he had chronic bronchitis.

Physical examination at the time of admission was productive of the following: The patient appeared to be in fairly good general health, but had numerous, discrete, apparently indolent, match-head to small cherry-size polymorphous lesions distributed as noted above (figures 1 and 2). Many were firm, erythematous papules while the

central portion of others was soft, fluctuant and contained purulent material. Some of the lesions had ruptured, with spontaneous evacuation of their contents, leaving central crater-like depressions, surrounded by a firm indurated ring, and a few, probably the earliest, had practically healed. The soft tissues about the proximal phalanx of the right great toe and left fourth finger, as well as those of the middle phalanx of the right fourth finger, were erythematous, swollen and tender. There was also evidence of long standing pulmonary emphysema.

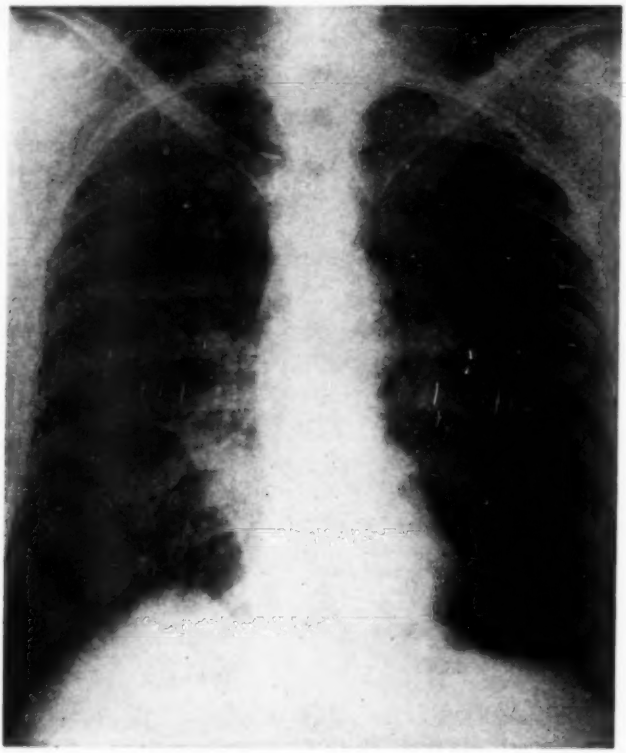
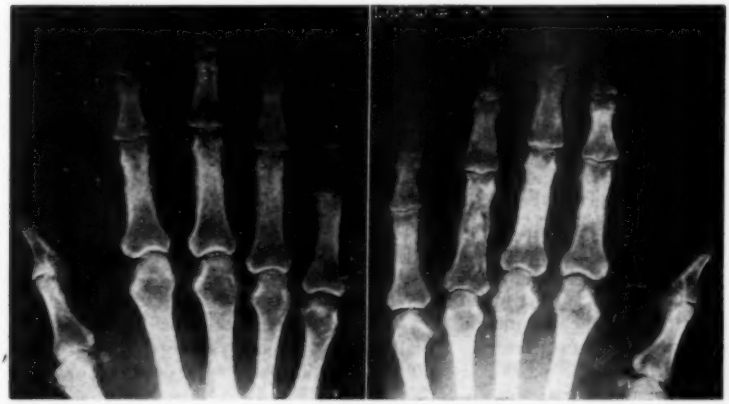


FIG. 3. The triangular shadow of increased density at the inferior border of the right hilum and tenting of the right diaphragm, illustrated here, persisted one year after all lesions of sporotrichosis had involuted being apparently related to atelectasis of the right middle lobe.

Roentgenograms were made of the hands, feet and chest. These demonstrated bilateral pulmonary emphysema of moderately severe degree, a triangular shadow of increased density at the inferior border of the right hilum and tenting of the right diaphragm (figure 3). Exact identity of the latter changes was indeterminate, although atelectasis of the right middle lobe was suspected. Destructive osseous changes involving the phalanges noted above were also apparent (figures 4 and 5). The roentgenologist was of the opinion that osteomyelitis, Boeck's sarcoid and metas-

tatic neoplasm could not be excluded from the realm of diagnostic possibilities as having induced the skeletal changes.

Tissue for microscopic examination was obtained from several lesions in various stages of evolution, and purulent material was aspirated from numerous intact pustules and inoculated on Sabouraud's medium. Pathologically most of the lesions showed a chronic process, with morphological features interpreted as those of mixed tuber-



FIGS. 4 and 5. Destructive changes apparently of sporotrichotic origin, involving the middle phalanx of the right fifth finger and proximal phalanx of the left fourth finger.

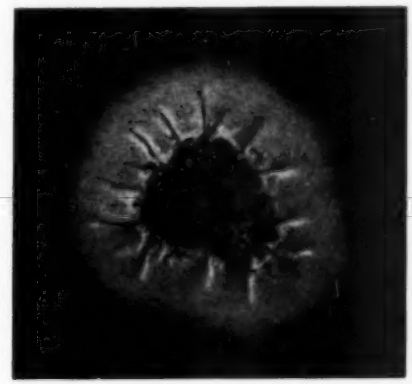


FIG. 6. The original colony of *S. schenkii* as cultured from the case recorded here. Note the convolutions. After three weeks the entire colony became darkly pigmented.

culous and pyogenic granulation tissue. Special stains did not reveal spirochetes, tubercle bacilli or evidence of fungi. All culture tubes and Petri dishes demonstrated the rather prompt growth of a sporotrichum which was identified after further definitive studies [2] as *S. schenkii* (figure 6). Comprehensive laboratory studies, with exceptions as noted above, were consistently negative.

Intensive and protracted therapy utilizing potassium iodide resulted in prompt and permanent involution of the cutaneous eruption. A roentgenogram of the chest approximately one year after his admission to the hospital showed the pulmonary findings to be unchanged, while roentgenograms of the hands and feet revealed that the osseous lesions had healed, leading to the suspicion that these latter were probably of mycotic origin, possibly secondary to deep seated cutaneous lesions in overlying soft tissues.

Summary

1. Sporotrichosis is a disease to be reckoned with on occasion by physicians in every branch of medicine. *S. schenkii* and *S. beurmanni*, of species within the genus sporotrichum, are the usual etiological agents. All species are frequent saprophytes, most often on vegetable material, but also at times on humans and on other animals. The disease probably develops in most instances because of a lessened resistance of the host at the time of inoculation.

2. Manifestations of the disease are polymorphous, this feature often being of diagnostic import especially as regards lesions of the skin. Although sporotrichosis is usually divided, for purposes of description, into the cutaneous and systemic types, it is worthy of note that a proponderance of all cases demonstrates involvement of the integument to a variable degree, and that demonstrable visceral lesions are most unusual. Of all the deep mycoses, sporotrichosis is the only one for which there exists a specific therapeutic agent.

3. An unusual case of multiple, disseminated, subcutaneous, gummatous sporotrichosis, with probable secondary osseous lesions is reported.

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THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN AND SODIUM PARA-AMINOHIPPURATE BY CONTINUOUS INTRAVENOUS DRIP *

By Robert Wall, M.D., *Washington, D. C.*, and Oliver Brundage, M.D., *Parkersburg, West Virginia*

The use of penicillin with and without heparin in the treatment of subacute bacterial endocarditis has justified the hope for temporary or permanent arrest of this disease. The addition of sodium para-aminohippurate as an enhancing agent may increase the effectiveness of penicillin therapy. Its use with penicillin in the treatment of subacute bacterial endocarditis has been reported by Loewe [1] and others with evident success.

Our patient was thought worthy of report because of: (1) the finding of a relatively resistant organism identified as *Streptococcus viridans*, (2) the large quantities of penicillin and para-aminohippurate administered, and (3) the apparent success of this treatment.

Case Report

J. W., a 50 year old white male, was admitted to the Bryn Mawr Hospital on June 5, 1946 with a history of fever, muscle aches, anorexia, shoulder pain, weakness, and dyspnea of seven weeks' duration.

On admission his temperature was 100° F., pulse 96, respirations were 22, and blood pressure was 140 mm. Hg systolic and 80 mm. diastolic.

At the age of 17 he had experienced an illness diagnosed as rheumatic fever by his family doctor. He was told that following this attack he was left with "leaky heart valves." Aside from slight dyspnea on exertion he led a normal life. Six years later, at the age of 23 years, he had another attack of rheumatic fever, this time of lesser severity. He was in bed for "only a few days." Fifteen years later, at the age of 38 years, he had still another attack of what was diagnosed as rheumatic fever. He was confined to bed again "for only a few days." During none of these attacks were there any signs or symptoms suggesting decompensation. He states that he was well following this last episode, 12 years before admission, until the present disease became apparent.

Seven weeks before admission to the hospital the patient observed that he felt weak, was losing his appetite, had vague muscle aches, and was more dyspneic than usual on exertion. At the time he was working as a foreman in a machine shop which required him to stand for long periods of time. When these symptoms presented he stopped work and remained in bed for the seven weeks preceding his admission to the hospital. He had evening temperature rises nightly to 102° to 103° F., which returned to normal in the morning. Ten days before admission he complained of neck and bilateral shoulder pain. His only medication at the time was sodium salicylate. Other than as already stated his previous medical history was negative.

On physical examination he was a pale, thin man resting in bed without marked distress. He was found to have an enlarged heart with harsh apical systolic and diastolic murmurs. His spleen and liver were not palpable and no petechiae were found.

His electrocardiogram showed a low T_2, negative T_3, and low T CR_5. A

* Received for publication July 21, 1947.

urinalysis showed a trace of protein and 50 to 60 red blood cells, which in later urinalyses were not observed. A blood culture taken on the day of his admission proved to be positive, containing *Streptococcus viridans*, which was reported to be "very sensitive to penicillin."

He was started on 500,000 units of penicillin daily by the intramuscular route by his attending physician. However, for some reason, after four days of this treatment the penicillin was stopped following a return of his temperature to normal. A blood culture taken one day later was reported negative and the patient was discharged apparently improved on June 18, 1946.

On arriving home the patient received the following treatment from his attending physician. Bi-weekly for three weeks he received 300,000 units of penicillin in beeswax for a total of 1,800,000 units of penicillin. He was then placed on oral penicillin with a daily dose of 300,000 units. This dosage was maintained for 73 days with a total of 21,900,000 units. As the patient again developed evening temperature rises despite this treatment he was again placed on sodium salicylate (60 gr. per week). The oral penicillin was discontinued. The sodium salicylate was administered for one week and as there was no response, the patient was again admitted to the Bryn Mawr Hospital on September 27, 1946, this time under ward care.

On readmission his temperature was 101° F., pulse 102, respirations were 22, and his blood pressure was 130 mm. Hg systolic and 70 mm. diastolic. His complaints at this time were fever, anorexia, weakness, and right shoulder pain which he attributed to the fact that he slept on his right side all the time, because sleeping on his left side made him "heart conscious."

On physical examination he appeared pale, thin, and anxious. His heart was enlarged and there were harsh apical systolic and diastolic murmurs. There were infrequent extrasystoles. The spleen and liver were not palpably enlarged, the upper border of liver dullness being at the fourth right intercostal space in the midclavicular line. No petechiae were found.

Positive blood cultures were obtained on the fifth, the eleventh, and the thirteenth days, each time demonstrating *Streptococcus viridans*. The sensitivity of the organism was tested, and it was found to be sensitive at the level of 0.5 unit per c.c. Penicillin was started by this time at a dosage of 1,000,000 units per day in saline. It was given mostly by the interrupted intramuscular route, but on three days the intravenous route was used in a solution of 1,000 c.c. 5 per cent glucose in normal saline solution. His temperature dropped to normal, and all treatment was stopped after 11 days.

Blood cultures were taken regularly and nine days after the cessation of penicillin treatment another positive blood culture was obtained and the organism identified as *Streptococcus viridans*. While waiting to obtain a supply of para-aminohippurate he was again placed on 1,000,000 units of penicillin daily by the interrupted intramuscular route to save his veins preparatory to continuous intravenous treatment.

Realizing the possible hazard of intravenous therapy in a cardiac patient, the following studies were performed. Phenolsulfonphthalein dye excretion test was 40 per cent. Urea clearance test showed 86 per cent normal. The plasma protein was 7.5 with 4.6 albumin and 2.5 globulin. The blood urea nitrogen was 11 mg. per cent. The prothrombin time was 90 per cent. The blood volume was estimated by the T–1824 (Evans Blue Dye) method and found to be 5,330 c.c. The expected blood volume for this patient was 5,370 c.c. The plasma volume was 3,518 c.c., and the cell volume was 1,812 c.c.

By this time the sodium para-aminohippurate * had been obtained and intensive intravenous treatment was initiated. During the treatment daily plasma samples were

* The authors wish to express their gratitude to Sharpe and Dohme, Inc., for the supply of sodium para-aminohippurate and their aid in performing the estimations of plasma penicillin levels.

taken each morning at the same time. This time coincided with the change of intravenous solutions.

In view of the resistance of the organism estimated at 0.5 unit per c.c., the approximate penicillin level needed in this case for the bactericidal effect was estimated according to the work of Loewe.[2] In his work he found serum assays of 0.1 unit per c.c. to be obtained by administering 100,000 units of penicillin per day by the continuous intravenous drip method. This would have made our optimum dosage 500,000 units, but as we had already learned that 1,000,000 units per day were insufficient to inhibit or kill the organism, we chose an arbitrary dose of 5,000,000 units per day.

Loewe [2] also found in his work on para-aminohippurate that when levels of PAH were *over* 10 mg. per cent he could obtain increases of penicillin levels three to six times that of the control. He estimated that to obtain PAH levels of 30 to 40 mg. per cent it was necessary to administer PAH at the rate of 150 mg. kg./hour. This would mean for our patient weighing 150 pounds that 245 grams in 24 hours would be necessary to gain 30 to 40 mg. per cent blood level of PAH. As our supply was limited and we wished to prolong the treatment as long as possible, we decided upon 200 grams as our daily dosage.

The plan of treatment was as follows:

For the first three days the continuous intravenous drip included daily:

(1) 5,000,000 units of penicillin
(2) 2,000 c.c. 5 per cent glucose in distilled water
(3) 50 mg. heparin (this was included merely to facilitate the mechanics of keeping a continuous intravenous drip running without clotting at the needle, and was not administered for any therapeutic value)

On the fourth day the solution was changed to include:

(1) 5,000,000 units of penicillin
(2) 2,000 c.c. 5 per cent glucose in distilled water
(3) 50 mg. heparin
(4) 200 grams of sodium para-aminohippurate

This was continued for 10 days.

The total quantity of penicillin over the 13 day period was 65 million units.

On the first day of PAH administration the patient experienced two involuntary bowel movements and complained of crampy abdominal pain of moderate severity. However, these reactions were not experienced after the first day of PAH administration. It was found that if the drip was sped up to the rate of 30 drops per minute or more, the crampy abdominal pains could be reproduced and as soon as the rate was returned to the desired rate of 20 to 22 drops per minute this pain was eliminated.

In addition to the 2,000 c.c. of fluid given in the intravenous drip daily, the patient was kept on a full house diet and allowed 1,000 c.c. of additional fluid by mouth. He was given maintenance doses of digitalis.

Following this treatment (figure 1) the patient was subjected to repeated blood cultures, all of which proved sterile. (The blood culture medium was infusion broth with added glucose, para-aminobenzoic acid, and penicillinase.) The urea clearance test was found to be 40 per cent normal. This was rechecked two months later and found to be 60 per cent normal. His temperature was constantly normal. His sedimentation rate, which had been a vertical curve before treatment, was starting to flatten out to a diagonal curve with a reading of 25 mm. in 60 minutes. He was fully compensated as to his cardiac state. His sole complaint was of right shoulder pain which has since responded to physiotherapeutic measures.

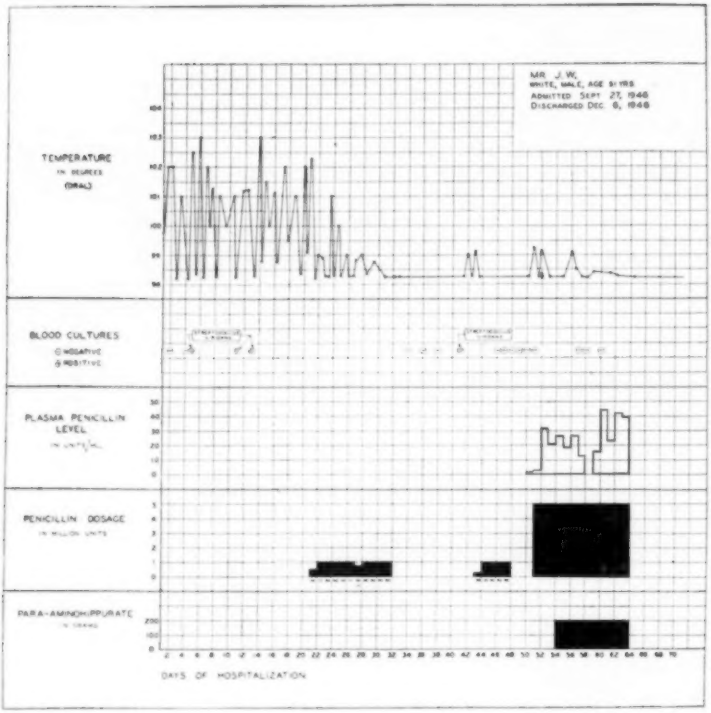

FIG. 1.

He was discharged eight days later. He was followed as an out-patient and seen every two weeks. At each visit he had a blood culture taken, all of which were negative. He was afebrile for six months. His sedimentation rate six months after discharge was a horizontal line reading 7 mm. in 60 minutes. He returned to work in a machine shop with no apparent difficulty in maintaining a full eight hour work day.

DISCUSSION

To administer 2,000 c.c. of solution by intravenous drip over 24 hours it was found that the rate had to be maintained at 20 to 22 drops per minute, and this quite naturally entailed constant supervision of the patient. It is also to be observed that this patient was unusually coöperative and bore the tedium of the 13 days of constant drip with remarkable patience. At times the position of the needle in the vein was not changed for 60 hours with no mechanical obstruction to the continuous flow of the solution.

Plasma penicillin levels taken daily on this patient were assayed by the Florey technic and did, when averaged for each period of treatment, show a definite

increase following the administration of PAH in conjunction with penicillin over the administration of penicillin alone.

On the eighth day of treatment the penicillin assay showed no penicillin present. Although this may be a laboratory error, it can surely not be dismissed as such. No explanation could be found for this.

Using the theoretical level of penicillin [2] calculated on 0.1 unit per ml. per daily dose of 100,000 units it will be found that practically all plasma penicillin levels were well over the theoretic level (table 1). The administration of 5,000-000 units of penicillin per day should yield, by theory, a level of 5.0 units per ml.

TABLE I

Plasma Penicillin Levels in Units/ml.

Day	Theoretical	Actual	Deviation		
1	5.0	2.3	−2.7		
2	5.0	31.6	26.6		
3	5.0	20.8	15.8	Total	−2.7 +42.4
4	5.0	27.0	22.0		
5	5.0	18.2	13.2		
6	5.0	27.0	22.0		
7	5.0	13.6	8.6		
8	5.0	0.0	−5.0		
9	5.0	16.1	11.1		
10	5.0	43.6	38.6		
11	5.0	22.3	17.3		
12	5.0	41.2	36.2		
13	5.0	39.2	34.2	Total	−5.0 +203.2

Granting that the use of PAH results in a higher penicillin blood level than when the same dose of penicillin is given alone, the authors question whether the difficulties and expense attendant upon prolonged intravenous administration of PAH are justified when the same high blood penicillin levels might be obtained by the use of larger penicillin dosages.

In reporting this case the authors realize full well that definite conclusions in evaluating the efficacy of any therapeutic regime cannot be drawn from one case report and so submit this case report to add to other cases similarly treated for overall evaluation in the future.

CONCLUSIONS

a. A case of subacute bacterial endocarditis due to *Streptococcus viridans* is presented.

b. Two previous attempts at penicillin treatment were unsuccessful in arresting the disease process.

c. The administration intravenously daily for 13 days of a solution containing 5,000,000 units of penicillin, plus 200 grams of sodium para-aminohippurate for the last 10 days of this treatment, is recorded as the treatment used. Heparin in small doses was added to facilitate the continuance of the constant venoclysis.

d. Plasma penicillin levels showed a definite increase over the expected estimated levels. On the average they were greater with the administration of sodium para-aminohippurate concurrently. However, the authors feel this same elevation could be effected more easily by merely increasing the penicillin dosage.

e. A follow-up of six months on this patient found him well and able to earn his living at his former occupation.

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EDITORIAL

GRADUATE EDUCATION IN ALLERGY

In a recent survey of hospital and medical college residencies and fellowships in allergy conducted by the Subcommittee on Graduate Education of the American Academy of Allergy it was found that 17 institutions in the United States offer facilities for this type of training. Of this group eight stated that it was difficult to attract high grade men. A consideration of this problem furnishes the basis of this report.

There would seem to be several reasons for this situation. Ignorance of the opportunities available for research and clinical training in allergy is one. Failure of the present facilities to attract is another. It is also probable that our courses in medical schools under-emphasize the importance of allergic diseases,[1] and as Barr [2] says, "it is more than deplorable that many young internists have been permitted to finish their training without contact

GRADUATE EDUCATION IN ALLERGY (FELLOWSHIPS AND RESIDENCIES)

	Council Approved	Number	Filled	Total Trained
1. Brooklyn Jewish Hospital	yes	3	2	10
2. Duke University Hospital	—	1	1	—
3. Johns Hopkins Hospital	yes	1	1	11
4. Mass. General Hospital (Harvard)	yes	1	0	9
5. Michigan University Hospital	—	3	3	12
6. Milwaukee County Hospital (Marquette)	yes	1	1	—
7. Montefiore Hospital (Pittsburgh)	yes	1	1	3
8. New York Hospital (Cornell)	—	1	1	2
9. Northwestern University	yes	2	1	2
10. Roosevelt Hospital	yes	2	2	7
11. University Hospital (N. Y. University)	yes	2	2	6
12. University of Illinois	yes	4	2	2
13. University of Pennsylvania Hospital	—	1	1	—
14. University of Virginia Hospital	yes	3	3	9
15. Veterans Hospital (Aspinwall, Pa.)	yes	2	2	2
16. Virginia Medical College	yes	2	2	2
17. Washington University (Barnes Hospital)	—	1	0	1
	12	31	25	78

with allergy and allergic thought." This is particularly true since few hospitals rotate their internes and assistant residents through the allergy clinic. The result has been that our best internes and residents, casting about for a field in which to do special study, have not had enough contact with the allergic diseases to be interested in them.

[1] SWINEFORD, OSCAR, JR.: Undergraduate education in allergy, Jr. Assoc. Am. Med. Coll., 1946, xxi, 265–270.

[2] BARR, D. P.: The relationships of allergy to medicine, Jr. Allergy, 1945, xvi, 61.

The table indicates the 17 hospitals and medical schools where fellowships and residencies in allergy are available. Of these, 12 have been approved by the Council on Medical Education and Hospitals of the A.M.A. and of the balance, four have applications in process. Twenty-five out of 31 openings are filled and the physicians trained through these facilities now number seventy-eight. The term in most instances is one year, generally renewable for one or two more years and the monthly stipend ranges from $50 to $280. In all cases there is close contact with the departments of Medicine or of Pediatrics and with the departments of Oto-Rhinology and of Dermatology. Opportunities for research are available and the resident is encouraged to interest himself in the basic sciences of Immunology and Bacteriology.

The individual pattern of the allergy services varies considerably. At the Brooklyn Jewish Hospital and at the Milwaukee County Hospital (Marquette) the residents live in the hospital, have the duties and responsibilities usually associated with a house officer, provide consultations on other services and attend the allergy clinic. At the University of Michigan Hospital, the residents in allergy are selected from the assistant resident and resident staff after three years of training in internal medicine or pediatrics. They serve as residents in allergy for two years, having the supervisory duties of a house officer and engaging in research and in undergraduate teaching. They have close contact with the general medical staff, the department of infectious diseases and the various specialty departments. At the University Hospital, New York (formerly the N. Y. Post-Graduate Hospital), the resident in allergy has charge of all allergy cases admitted from the adult allergy clinic and engages in research, the activities of the Allergy Clinic and related departments, and is also assigned to the department of Immunology and Bacteriology for additional work. He is required to continue his contact with internal medicine by attending medical out-patient clinics and conferences. The same program is in most respects followed by the Montefiore Hospital (University of Pittsburgh), University of Virginia Medical College Hospital, the Veterans Hospital (Aspinwall) and Virginia Medical College.

In a number of institutions the work is more characteristic of a research fellow with added training in clinical medicine, the specialties related to allergy and the fundamental departments of Immunology and Bacteriology. In these institutions there is less clinical responsibility on the in-patient services, the emphasis being placed upon research. Barnes Hospital (Washington University), Duke University Hospital, Johns Hopkins Hospital, Massachusetts General Hospital (Harvard), New York Hospital (Cornell), Northwestern University Medical College, Roosevelt Hospital (New York), University of Illinois, and University of Pennsylvania Hospital, follow this pattern. Some of these institutions offer post-graduate education and in this group the University of Illinois and the University Hospital of New York University are examples.

In spite of these well integrated and well planned programs, the oppor-

tunities are not attracting many high grade men. The development of graduate education in allergy is only a small part of the problem of graduate education in general. The relative absence of organization of the graduate educational facilities in our hospitals and medical schools, as compared with the courses developed for undergraduate and post-graduate education, is recognized by the Commission on Graduate Education.[3] Undergraduate medical education and post-graduate courses are largely supported by student fees and university endowments, whereas education at the resident and fellowship level is for the most part dependent upon grants for special projects. Most hospitals have trouble enough to meet their necessary expenses without appropriating additional funds for what primarily amounts to an educational program. The donors of funds have placed too much emphasis on research in the laboratory and too little, especially in the field of allergy, on the development of young men whose training is primarily clinical. It is rather paradoxical to see large endowments of medical schools devoted to the training of future physicians carefully selected for outstanding qualities of leadership and then, having provided such a preëminent educational experience, fail to establish opportunities for hospital or fellowship training in which these qualities for leadership can be activated for outstanding service.

It is important to discourage undue specialization, but it is also true, especially in internal medicine, that no physician can know completely the ramifications of its important subdivisions notably allergy, infectious diseases, psychosomatic medicine, cardiology, peripheral vascular disease, hematology, metabolism, endocrinology and the special diseases of the lungs and gastrointestinal tract. Instead of leaving to chance the selection by residents and fellows of one of these smaller divisions, would it not be the part of wisdom and foresight for the leading medical institutions to group these various specialties and organize them for graduate education? Allergy would fit well into a group comprising also infectious diseases, immunology and psychosomatic medicine. Similar associations comprising cardiology, peripheral vascular disease and hematology, or metabolism and endocrinology, are desirable and are necessary if young men are to be trained in strategic centers for leadership in teaching, research and consultation practice.

In the future development of allergy, emphasis will be placed on the widening scope of hypersensitivity in disease, not only to include the common allergic ailments but also the wide variety of tissue changes due to sensitization as exemplified by the researches of Landsteiner, Rich, Klemperer and others. The young man choosing allergy as a subspecialty will consider himself a part of the whole field of applied immunology. Yet, fundamentally, as Cooke[4] points out, "Education in allergy must be based upon

[3] Graduate Medical Education, Report of the Commission on Graduate Education, 1940, Univ. of Chicago Press, page 14.

[4] Cooke, R. A.: Allergy in relation to medical education, Clinics, 1946, v, 322.

and follow a thorough training in the broad field of internal medicine or pediatrics." To divert the resident or fellow into allergy without such preliminary training will defeat the prime purpose of graduate education in allergy, which is to furnish for teaching, research and practice, men who will not only be familiar with the concepts of hypersensitivity and immunology but will also understand their clinical application.

HORACE S. BALDWIN, M.D.,
Chairman of Sub-committee on Graduate Education, American Academy of Allergy,

and

W. C. SPAIN, M.D., F.A.C.P.,
Chairman of Committee on Education, American Academy of Allergy

REVIEWS

Textbook of the Rheumatic Diseases. Edited by W. S. C. COPEMAN, O.B.E., M.D., F.R.C.P. 612 pages; 17 × 24.5 cm. The Williams and Wilkins Co., Baltimore 2, Md. 1948. Price, $12.50.

Dr. Copeman has given his volume the title, "Textbook of Rheumatic Diseases." In so doing he has stated a purpose which the text has fulfilled admirably. The book expresses the British point of view, particularly in that the author gives "non-articular rheumatism" more prominence than do American students of the subject. Perhaps English experience warrants this, but fibrositis is not so frequent in its occurrence as a recognizable entity in this country. On the other hand with the rise of psychosomatic medicine, psychogenic rheumatism occupies a much more prominent place in America than this English volume allots to it. However, the correctness of either view is not yet established.

The arrangement of the textbook in devoting so much discussion to the anatomy and what is known concerning the physiology of joints, as well as the relation of other tissues to rheumatic diseases, affords an introduction and background to the field which is most desirable and often is lacking. This not only prepares one for the clinical manifestations of joint disease but guides one naturally to the discussions of the pathology of joint disease, which is presented in a coördinated fashion. The chapters on pathology are to be particularly commended to the reader. They present this sparse field, in which information, either ante-mortem or post-mortem is so difficult to obtain, in a manner which suggests the interrelationship of the various forms of inflammatory joint disease but hardly emphasizes this relationship sufficiently. Likewise in the clinical chapters on inflammatory joint disease this possible, if not probable, close linkage could be more extensively dwelt upon. Perhaps the collective authorship, which gives much that is to be desired in that each phase is dealt with by one of large experience in the particular subject at hand, is in a measure responsible for this. So often with this arrangement coördinated relationship fails to develop, which seems to be the case here. Many times the treatise suffers when handled in this manner. For instance, disseminated lupus erythematosis is mentioned in a short section under the heading, "Other Pathological Conditions Simulating Arthritis," and by another author in discussing "Serological Reactions with Haemolytic Streptococci" mention is made that—"Results with non-rheumatic controls were weak or doubtful except in psoriasis and lupus erythematosis." Whereas the relationship of rheumatoid arthritis or Still's disease, or for that matter, even rheumatic fever to disseminated lupus, is by no means established, much less understood, it is nevertheless too strongly suggested both clinically and pathologically to be passed over so lightly.

In dealing with the affections of the shoulder joint, the author has attempted to bring about some clarification of the maze of conditions which are so freely brought together under the heading of "Brachial Neuralgia." Any effort toward this end is laudable and he not only has seen the need for this, but has gone a long way toward more accurate diagnosis. Likewise with the sciatic nerve, he resists the tendency of the day to attribute most, if not all, sciatic pain to the protrusion of a ruptured intervertebral disc, and accords to other affections of this area their proper place. This effort to combat looseness in diagnosis is sorely needed, for rheumatic diseases in general suffer from this lack of accurate differentiation.

The chapter dealing with "The Radiology of the Rheumatic Diseases" again strives for clarity and the emphasis given to early bone and joint changes is of particular value. We are prone to consider the radiological diagnosis of gout as readily made if any changes are present, but the author has realized the confusion that may

arise both in the differentiation from the changes of rheumatoid arthritis and more particularly those instances of atypical rheumatoid arthritis where either a monarthritis or recurring brief and sharply defined attacks lead to clinical difficulties. He is quite aware of the tendency to consider early changes as lacking or unrecognizable and appreciates the desirability of early detection of rheumatoid arthritis as such, when a cessation of activity would leave a joint at least functionally intact. These early changes are pointed out and in an unusually well illustrated chapter much is contributed to this early diagnosis, so much to be desired.

The section concerned with physical therapy and the orthopedic problems of rheumatic diseases is excellent. Here the author stresses the importance of the prevention of deformity which the patient is willing to dispense with because it is painful and the doctor is so prone to overlook. Likewise the indications and contraindications are made clear, as well as what may be expected of the various types of physical therapy. This is an important contribution. The function of the orthopedic surgeon in the prevention of deformity is properly stressed, which adds much to a coördinated approach to rheumatic diseases and broadens the appreciation of the problem. In rheumatoid arthritis, for example, this more comprehensive approach makes both doctor and patient aware of the fact that it is the results of the disease which impose the crippling deformities, that the joint has no working margin and when a joint is inflamed by so much is its function limited.

The arrangement of the volume is good, the index is well arranged and makes the information contained in the text readily accessible, and the illustrations are extremely well done and add much to the clarity of the text. The author is to be congratulated upon his efforts and, except for the somewhat disconnected approach to the problem of inflammatory joint disease of unknown etiology, has made a valuable contribution. Here, again, this may be only a matter of point of view.

CHARLES W. WAINWRIGHT

Bone Marrow Biopsy: Haematology in the Light of Sternal Puncture. By S. J. LEITNER, M.D. English Translation Revised and Edited by C. J. C. BRITTON, M.D., Ch.B., D.P.H., and E. NEUMARK, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P. 433 pages with 7 plates (6 in color) and 194 text-figures. 24.5 × 16 cm. Grune & Stratton, New York. 1949. Price, $8.50.

This work is an English translation of the recent second Swiss edition of Leitner's monograph. It is based on investigations carried out at the medical clinic of the University of Berne and the first edition was published in the Folia Haematologica in 1941. The wider use of sternal puncture in clinical study has in recent years brought forth much that is new and, in some instances, has changed the entire hematological aspect of certain diseases. In his second edition Leitner has succeeded in a complete modernization of his material, keeping well apace with all that is new and worthwhile in hematology.

The rather urgent need for a really comprehensive work on the bone-marrow has been recognized by all hematologists, clinicians and pathologists. It is interesting that the translator, Britton, discloses that he himself was working on such a volume when asked to review and edit this work. It is still true today that, at least in certain fields of hematology, the Continental and Anglo-American schools of thought vary rather widely. Hence, it is fortunate that Britton was given wide discretion by the author in editing, alteration and the incorporation of new material. The net result is pleasing to the American reader who seldom is disturbed by the "foreign" flavor he is ingesting.

Despite the very specialized nature of this study the author well realizes the impossibility of divorcing bone-marrow biopsy from the history, examination and

other laboratory findings in any given hematological case. Accordingly, in the description of the blood dyscrasias, adequate clinical data are incorporated when pertinent. In fact, 81 illustrative case histories are included. The author's cell terminology throughout the treatise cannot be criticized if for no other reason than that, for a long time, blood cell terminology has been in complete chaos. Some hope for the future is offered in that, at this writing, active efforts in America are being taken to try to secure a single accepted terminology.

The quality of the illustrations in this volume is adequate. As to number, the reader of a work of this type is hungry for illustrations and the inclusion of even double the quantity would not have surfeited the earnest student.

Despite minor short-comings, such as the inclusion of English but utter omission of American workers who first revealed the clinical implications of the Rh factor, the work is sound and reliable. Not particularly because of the paucity of monographs on this subject but because of its intrinsic worth, this book should be acquired by the practicing hematologist to add to his comfort in his daily stint with problems of the bone marrow.

H. R. P.

Practical Aspects of Thyroid Disease. By GEORGE CRILE, JR., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic. 355 pages, 20.5 × 14 cm. W. B. Saunders Co., Philadelphia. 1949. Price, $6.00.

The author's stated purpose is to present diseases of the thyroid in such a way that the physician may gain a better understanding of the aims of the surgeon, and that the surgeon may better appreciate what the internist and radiologist can accomplish. This purpose is admirably achieved. Dr. Crile strikes a nice balance between medical and surgical opinion and between new and conservative measures, in a way which gives the reader great confidence in the author's judgment.

The whole field of thyroid disease is covered. The diagnosis of hyperthyroidism and its treatment with iodine, antithyroid drugs, roentgenotherapy and radioactive iodine, are well and fully discussed. Its treatment by thyroidectomy is handled in detail with full description and discussion of preoperative management, anesthesia, technic of operation, postoperative care, complications and results. The author emphasizes the advantages of extracapsular ligation of the inferior thyroid artery. Eighty pages are devoted to malignant diseases of the thyroid, while further chapters deal with endemic goiter, intrathoracic goiter, recurrent hyperthyroidism, congenital abnormalities of the thyroid, and thyroiditis.

This book can be recommended to physician, surgeon, and student. It lives up to its title in being essentially practical with theorizing reduced to a minimum. The format is excellent, and the text well written and easily read. One minor criticism concerns punctuation. Many four, five, or even six line sentences, piling up their clauses, are allowed to ride on to their conclusion without a comma. Small though this complaint is, comfort-stops, at proper intervals, make a great difference to the reader's journey.

H. J. L. M.

Food Poisoning. Revised Edition. By G. M. DACK, Ph.D., M.D., Professor of Bacteriology and Director, Food Research Institute, University of Chicago. 184 pages; 15.5 × 23.5 cm. The University of Chicago Press, Chicago 37, Ill. 1949. Price, $3.75.

This is an excellent review of the epidemiology, symptomatology, cause, and prevention of the common types of gastro-enteritis. It is much more than a mere

enumeration of the poisons and toxins which man can ingest with his food. Each type is discussed in full with illustrative histories. One fascinating record of poisoning is that of a man who, while gorging on mussels which he had just caught, negligently gave a few to a dog which shortly thereafter vomited; to a cat which developed paralysis the next day, and to two kittens which died. The patient himself developed only some nausea and a general numbness around his lips.

Here, too, is an adequate coverage of poisonous plants such as trematol or milk sickness which produces "trembles" in cattle and may produce death in man despite pasteurization which does not destroy the toxin.

Staphylococcal food poisoning is well demonstrated to be due to an enterotoxin elaborated by certain strains of staphylococci with a sudden onset and rapid severe prostration. In contrast, the essentially infectious nature of salmonella outbreaks is substantiated. These two types are well and adequately covered.

A final chapter on causes of gastro-enteritis other than those ordinarily thought of as food poisoning is particularly helpful and is up to date in its summary of bacterial and viral causes.

This book will be useful to every physician.

F. B. B.

Encyclopedia of Medical Sources. By EMERSON CROSBY KELLY, M.D., F.A.C.S 476 pages; 16 × 23.5 cm. The Williams and Wilkins Company, Baltimore. 1948 Price, $7.50.

As Editor of "Medical Classics," the author is eminently qualified for the task of preparing such a volume as this encyclopedia of medical sources. While some modern teachers frown upon the association of proper names with signs, operations, syndromes, etc., the historical value of such association is unquestioned. In addition, since medical literature still contains references to proper names, this volume is of real importance.

The author has produced an admirably useful cross-reference volume of medical sources. A list of the authors' names in bold-face type, together with the title and complete reference to their earliest or best work, comprises the main section, and an index lists the medical terms. It is stated in the preface that about 95 per cent of the papers listed have been consulted in the original. Following each author's name there is a notation of his nationality, his field of work, and his year of birth and death; then the syndrome, reaction, test, operation or other contribution is listed, together with the complete title and reference of the article or articles.

Although such a volume cannot be absolutely complete, the author is to be warmly congratulated upon his compilation. He has performed a great service to the medical and allied professions. Physicians, students, research workers, medical historians, and librarians will find this encyclopedia most helpful.

J. E. S.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

An Atlas of Bone-Marrow Pathology. By M. C. G. ISRAELS, M.Sc., M.D., M.R.C.P., Lecturer and Deputy Director, Department of Hematology, The University and Royal Infirmary, Manchester, etc. 79 pages; 25 × 19 cm. 1948. Grune & Stratton, Inc., New York. Price, $6.50.

Atlas of Oral and Facial Lesions, and Color Film Library. By RALPH HOWARD BRODSKY, D.M.D., Consulting Oral Surgeon, Department of Hospitals, New York City, etc. With a Foreword by LEROY M. S. MINER, M.D., D.M.D., Formerly Dean, Harvard University Dental School. 127 pages, with slide case containing 100 colored slides; 26 × 17.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $80.00.

Cardiac Catheterization in Congenital Heart Disease: A Clinical and Physiological Study in Infants and Children. By ANDRÉ COURNAND, M.D., Associate Professor, Department of Medicine, College of Physicians and Surgeons, Columbia University; JANET S. BALDWIN, M.D., Assistant Professor, Department of Pediatrics, New York University College of Medicine, and AARON HIMMELSTEIN, M.D., Instructor, Department of Surgery, College of Physicians and Surgeons, Columbia University. 108 pages; 28.5 × 20.5 cm. 1949. The Commonwealth Fund, New York. Price, $4.00.

Coronary Artery Disease. By ERNST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City, and NORMAN F. BOAS, M.D. 399 pages; 21 × 14.5 cm. 1949. Year Book Publishers, Inc., Chicago. Price, $6.00.

Diagnosis of Viral and Rickettsial Infections: Symposium Held at the New York Academy of Medicine January 29 and January 30, 1948. Edited by FRANK L. HORSFALL, JR. 153 pages; 23.5 × 15.5 cm. 1949. Columbia University Press, New York. Price, $3.75.

Diseases of the Liver, Gallbladder and Bile Ducts. 2nd edition, revised. By S. S. LICHTMAN, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Cornell University Medical College, etc. 1135 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, $18.00.

Das Elektrokardiogramm: Ein Handbuch für Theorie und Praxis. By DR. EUGEN LEPESCHKIN, Balneologisches Institut, Bad Nauheim. 336 pages; 24 × 16 cm. (paper-bound). 1947. Verlag Von Theodor Steinkopff, Dresden and Leipzig.

The Epidemiology of Hemolytic Streptococcus During World War II in the United States Navy. By ALVIN F. COBURN, M.D., The Rheumatic Fever Research Institute, Northwestern University Medical School, and DONALD C. YOUNG, M.D., Medical Director, Communicable Disease Service, Herman Kiefer Hospital. 229 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $4.00.

Evaluation of Chemotherapeutic Agents: Symposium Held at the New York Academy of Medicine, March 25 and 26, 1948. Edited by COLIN M. MACLEOD. 205 pages; 23.5 × 15.5 cm. 1949. Columbia University Press, New York. Price, $4.00.

Food Poisoning. Revised Edition. G. M. DACK, Ph.D., M.D., Professor of Bacteriology and Director, Food Research Institute, The University of Chicago. 184 pages; 23.5 × 15.5 cm. 1949. The University of Chicago Press, Chicago. Price, $3.75.

The Fundamentals of Pulmonary Tuberculosis and Its Complications for the Student, the Teacher, and the Practicing Physician. Sponsored by the AMERICAN COLLEGE OF CHEST PHYSICIANS. Editor: EDWARD W. HAYES, M.D. Editorial Committee: ANDREW L. BANYAI, M.D., HERMAN HILLEBOE, M.D., J. ARTHUR MYERS, M.D., and J. WINTHROP PEABODY, M.D. 480 pages; 24 × 16 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $9.50.

The Invert and His Social Adjustment. 2nd ed. By ANOMALY, to which is added a Sequel by the same author; with an Introduction by R. H. THOULESS, M.A., Ph.D. 290 pages; 17.5 × 10.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $3.00.

Kayne, Pagel, and O'Shaughnessy's Pulmonary Tuberculosis: Pathology, Diagnosis, Management and Prevention. 2nd Edition. Revised and partly rewritten by WALTER PAGEL, M.D., Pathologist, Central Middlesex County Hospital, London; F. A. H. SIMMONDS, M.A., M.D., D.P.H., Medical Director, Clare Hall County Hospital, Middlesex; N. MACDONALD, M.B., M.R.C.P.Ed., Physician to the Chest Clinic, Redhill County Hospital, Middlesex, and L. FATTI, F.R.C.S., Thoracic Surgeon, Hillingdon County Hospital and Harefield County Hospital, Middlesex. 720 pages; 25 × 17.5 cm. 1949. Oxford University Press, New York. Price, $18.50.

Medical X-ray Protection Up to Two Million Volts. Handbook 41. Written by a sub-committee of the National Committee on Radiation Protection. 43 pages; 20 × 13 cm. (paper-bound). 1949. National Bureau of Standards, U. S. Department of Commerce, Washington, D. C. Price, 15 cents.

Observations on the Pathology of Hydrocephalus. Medical Research Council Special Report Series No. 265. By DOROTHY S. RUSSELL. 138 pages; 24.5 × 15 cm. (paper-bound). 1949. His Majesty's Stationery Office, London. Price, Six shillings, net.

Operative Surgery. By FREDERICK C. HILL, B.A., M.S. (Surg.), M.D., Associate Professor of Surgery, The Creighton University School of Medicine, Omaha; Foreword by CHARLES W. MAYO, B.A., M.S. (Surg.), M.D., Section on Surgery, Mayo Clinic, Rochester. 698 pages; 24.5 × 16 cm. 1949. Oxford University Press, New York. Price, $12.75.

Die Permeabilitätspathologie Als Die Lehre Vom Krankheitsbeginn. By PROF. DR. HANS EPPINGER. 755 pages; 25.5 × 18 cm. (paper-bound). 1949. Springer-Verlag, Vienna. Price, Sch. 28.50; bound, Sch. 29.40.

A Primer of Electrocardiography—2nd edition, revised. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc., and TRAVIS WINSOR, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California Medical School, etc. 245 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, $4.50.

Some Common Psychosomatic Manifestations. By J. BARRIE MURRAY, M.A., M.D. (CANTAB.), M.R.C.P., Diagnostic Physician, Tavistock Clinic, etc. 101 pages; 18.5 × 12.5 cm. (paper-bound). 1949. Oxford University Press, New York. Price, $2.50.

The Uses of Penicillin and Streptomycin—Porter Lectures, Series 15. By CHESTER SCOTT KEEFER, M.D., Wade Professor of Medicine, Boston University School of Medicine, etc. 72 pages; 22 × 14 cm. 1949. University of Kansas Press, Lawrence, Kansas. Price, $2.00.

Veterans Administration Technical Bulletins—Series 10, Volume II, 1948. 183 pages; 27 × 20.5 cm. January, 1949. Veterans Administration, Washington. Price, Not for sale—limited edition for distribution to VA hospitals and medical libraries.

WILLIAM S. MIDDLETON, M.D., Sc.D., F.A.C.P., Madison, Wis.,
President-Elect, The American College of Physicians

(See following page for biography)

COLLEGE NEWS NOTES

William Shainline Middleton, M.D., Sc.D., F.A.C.P., Madison, Wis., President-Elect, The American College of Physicians

Born, Norristown, Pa., January 7, 1890; M.D., 1911, University of Pennsylvania School of Medicine; Instructor in Medicine, 1912–1915, Assistant Professor of Medicine, 1915–1923, Associate Professor of Medicine, 1923–1933, Professor of Medicine, 1933 to date, and Dean, 1935 to date, University of Wisconsin Medical School; Physician, State of Wisconsin General Hospital since 1935; Diplomate and for many years Secretary-Treasurer, American Board of Internal Medicine; Fellow of the American College of Physicians since 1929.

Dr. Middleton has had an illustrious career, characterized by outstanding service to medical education, medical science and the Medical Corps of the U. S. Army. He is the author of a great host of published articles appearing in leading journals over the country. During World War II, with the rank of Colonel, he served with great distinction as the Chief Consultant in Medicine in the European Theater of Operations of the U. S. Army.

Besides being a member of his county and state medical societies, he is a Fellow of the American Medical Association, a member of the Association for Clinical Investigation, Central Society for Clinical Research, an honorary foreign member of the Association of Physicians of Great Britain and Ireland, a Fellow of the Royal College of Physicians of London, an honorary Fellow of the Royal Society of Medicine and a member of the Association of American Physicians. During the years he was the Secretary-Treasurer of the American Board of Internal Medicine, he made outstanding contributions to the development of that Board at a time when the work of the Board was expanding most rapidly.

He has served the American College of Physicians as a Regent since April 1, 1944, and as a member of many of its most important and active committees. He served as First Vice President for the year 1948–1949 and was elected President-Elect at the New York Annual Session on March 31, 1949. He will assume office as President at the Thirty-First Annual Session to be held at Boston, Mass., during April 1950.

The Postgraduate Course Program of the American College of Physicians

Since the Annual Session of the American College of Physicians in New York the latter part of March, four additional courses on the spring schedule have been concluded.

Course No. 5, "Electrocardiography: Basic Principles and Interpretation," was given at the Massachusetts General Hospital, April 25–30, 1949, under the Directorship of Dr. Conger Williams. The course, limited to 25 registrants, was filled to capacity and a large number of members could not be accommodated. Those who took the course have reported most enthusiastically upon its great worth.

Course No. 6, "Diseases Caused by Immune Mechanisms," was given under the combined auspices of the American College of Physicians and the University of Pittsburgh School of Medicine, at Atlantic City, April 28–May 1, 1949, under the Directorship of Dr. Leo H. Criep. This course also was registered to its capacity of 50, and although it was condensed into four days, those in attendance have indicated an unanimous and enthusiastic endorsement of all features of the course.

Course No. 7, "Cardiovascular Disease," was given in coöperation with various Philadelphia institutions and the American College of Physicians at the College Headquarters in Philadelphia, May 2–7, 1949, under the Directorship of Dr. William G. Leaman, Jr., F.A.C.P. Ninety-two physicians were registered, and the course was one of the most successful in this field the College has ever organized.

Course No. 8, "Physiological Basis for Internal Medicine," under the joint sponsorship of the American College of Physicians and the University of Pennsylvania Graduate School of Medicine, was given at Philadelphia, May 9–14, 1949, with a registration of 244 physicians. Obviously the instruction had to be of a didactic character with so large a group, but this course, regularly appearing on the College schedule, is probably the most popular course ever organized by the College. Dr. Julius H. Comroe, Jr., F.A.C.P., Professor of Physiology and Pharmacology in the University of Pennsylvania Graduate School of Medicine, was the Director.

Yet remaining on the spring schedule is Course No. 9, "Endocrinology," to be given at Tufts College Medical School, Boston, June 13–18, 1949, under the Directorship of Dr. Edwin B. Astwood, F.A.C.P. At the time of the preparation of this notice, there appears to be a wholly satisfactory registration developing. This course is designed for internists who are specially interested in Endocrinology and who desire further training in the basic physiology and biochemistry of the subject.

The Autumn, 1949, Proposed Schedule

The Advisory Committee on Postgraduate Courses and the Board of Regents have approved the following proposed schedule of courses for the autumn of 1949, but in not all instances have the directors accepted and the arrangements been concluded; neither have the dates in all instances been set. However, early in July the Postgraduate Bulletin will be published and mailed to all members and to all others requesting copies.

(1) Internal Medicine. One week; University of Minnesota Medical School; Dr. George N. Aagaard, Director of Postgraduate Education, and Dr. Cecil J. Watson, F.A.C.P., Director of the course.

(2) Preclinical Science in Internal Medicine. One week, October 24–29, 1949; Washington and St. Louis Universities, St. Louis, Mo.; Dr. Ralph A. Kinsella, F.A.C.P., and Dr. W. Barry Wood, F.A.C.P., Directors.

(3) Internal Medicine. One week; University of Wisconsin Medical School, Madison, Wis.; Dr. William S. Middleton, F.A.C.P., Director.

(4) Cardiology. One week; Massachusetts General Hospital; Dr. Paul D. White, F.A.C.P., Dr. Howard B. Sprague, F.A.C.P., and Dr. Edward F. Bland, Co-Directors.

(5) Cardiology. Two weeks; National Institute of Cardiology of Mexico, Mexico City; Dr. Ignacio Chavez, F.A.C.P., Director. This course may be delayed until sometime during 1950 and given as a summer course, in which the class will meet from 9:00 to 1:00 daily, and the rest of the day be free for vacation or other purposes.

(6) Cardiology. One week; University of Southern California Medical School, Los Angeles, Calif.; Dr. George C. Griffith, F.A.C.P., Director. Dr. Griffith has accepted the directorship, but has not specified the date.

(7) Clinical Neurology. One week, October 17–22, 1949; Jefferson Medical College of Philadelphia; Dr. B. J. Alpers, F.A.C.P., Director.

(8) Hematology. One week; Boston institutions. Dr. William B. Castle, F.A.C.P., has been requested to act as Director, but the course may have to be

delayed until sometime in 1950, due to autumn commitments which may interfere with Dr. Castle's organizing and directing the course.

(9) GASTRO-ENTEROLOGY. One week; University of Chicago; Dr. Walter L. Palmer, F.A.C.P., Director.

(10) PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. One week; Tulane University of Louisiana School of Medicine, New Orleans, La.; Dr. George E. Burch, Jr., F.A.C.P., Director.

APPLICATIONS BEING RECEIVED FOR THE AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS, 1950–1951

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1950 to June 30, 1951. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1949. Announcement of awards will be made November, 1949.

REGENTS OF THE COLLEGE TO AUTUMN MEETING NOVEMBER 12–13, 1949

President Reginald Fitz, Boston, has designated the date of November 12–13 for the next meeting of the Board of Regents of the American College of Physicians. The Credentials Committee will meet on November 11–12, and other important Committees will likewise meet on November 12.

Proposals of candidates for membership must be filed 60 days in advance of action. Therefore, September 12 is the closing date for receipt of proposals of candidates for action at this meeting.

ADDITIONAL LIFE MEMBERS

The American College of Physicians gratefully acknowledges recent subscriptions to Life Membership by the following Fellows of the College:

Walter L. Bierring, Des Moines, Iowa.
William V. Conn, Greensburg, Pa.
Robert M. Moore, Indianapolis, Ind.
Arthur W. Phillips, Philadelphia, Pa.
Clark P. Pritchett, Columbus, Ohio.
Samuel J. Schneierson, New York, N. Y.
Clarence H. Webb, Shreveport, La.

SPECIALTY BOARD FORMED PREVENTIVE MEDICINE AND PUBLIC HEALTH

With approval received on February 6, 1949, from the Advisory Board of Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association, the American Board of Preventive Medicine and Public Health, Inc., began the work of certifying to the qualifications of physicians in these closely

related fields. Among the first officers of the new Board are the following Fellows of The American College of Physicians: Walter L. Bierring, M.D., Des Moines, Iowa; Felix J. Underwood, M.D., Jackson, Miss.; and James S. Simmons, M.D., Boston, Mass. Colonel Don Longfellow, (MC), U. S. A., F.A.C.P., and George R. Callender, M.D., F.A.C.P., Chief of the Pathology Division of the Veterans Administration, both of Washington, D. C., are Consultants to the Board from the Federal Services.

The membership of the Board represents the American Public Health Association, The American and Canadian Public Health Associations, The Association of Schools of Public Health, The Southern Medical Association, and the Section on Preventive and Industrial Medicine and Public Health of The American Medical Association, as well as practitioners of the specialties.

The Board is authorized to grant certification without examination to a "Founder's Group," defined to include Professors and Associate Professors of Preventive Medicine and Public Health in approved schools of Medicine or Public Health, or individuals who have been Presidents of the sponsoring societies, or practitioners who have had ten years or more of distinguished service in the field and are held to be eligible by the Board. Otherwise, certification is by examination. The requirements are as follows: moral and ethical standing; graduation from an approved United States or Canadian Medical School, or from a satisfactory foreign Medical School; an internship of one year or more in an approved or satisfactory hospital; licensure in the U. S. A. or Canada; special training in Preventive Medicine or Public Health, including at least six years of special training or practice in Preventive Medicine and Public Health, including at least one academic year of graduate study leading to the Degree of Master of Public Health, or a satisfactory equivalent, and field training or acceptable residency in the specialty of at least two years; limitation of practice to the teaching or practice of Preventive Medicine or Public Health.

Examinations will be in two parts; the first consisting of a comprehensive written examination; the second part being an oral or practical examination. Applications for examination must be filed with the Secretary of the Board at least 90 days before the date of examination on prescribed application forms accompanied by photographs of the applicant, letters of endorsement, and the application fee. The application fee is $15.00, not returnable, and the certification fee is $35.00.

The first examinations of the Board were held in Washington, D. C., May 14–16, 1949. The next examinations are scheduled to be held in New York City, October 22–24, 1949. Notices of future examinations will appear in this publication.

Requests for further information concerning the requirements and activities of the Board and applications for admission to examinations should be addressed to Ernest L. Stebbins, M.D., Secretary-Treasurer, The American Board of Preventive Medicine and Public Health, Inc., 615 N. Wolfe St., Baltimore 5, Md.

The Chicago Medical Society will offer a course in CARDIO-RENAL and PERIPHERAL VASCULAR DISEASES October 17–22, 1949. The faculty will include leading teachers from all over North America and the course will comprise lectures, question periods, round tables, and informal conferences. The location will be Thorne Hall, Northwestern University Medical School, Chicago, and registration will be limited to 100. Information may be secured from Willard O. Thompson, M.D., F.A.C.P., Chairman, Committee on Postgraduate Medical Education, Chicago Medical Society, 30 North Michigan Avenue, Chicago 2, Ill.

The American Trudeau Society coöperating with the University of Colorado School of Medicine will offer a Postgraduate course in PULMONARY DISEASES and

THORACIC ANESTHESIOLOGY at the University of Colorado Medical Center, Denver, July 18–30, 1949. Registration is limited to physicians from Colorado, North and South Dakota, Nebraska, Kansas, New Mexico, Arizona, Utah, Wyoming, and Montana, and to physicians who have a special interest in the subject of the course. The registration fee is $100.00. A complete outline of the course, application blanks, and other information may be secured by writing to the American Trudeau Society, 1790 Broadway, New York 19, N. Y.

THE KAPPA DELTA AWARD FOR RESEARCH IN ORTHOPAEDIC SURGERY

The National Council of the Kappa Delta Sorority has inaugurated a prize of $1,000.00 to be given annually by the American Academy of Orthopaedic Surgeons for the best research in orthopaedic surgery performed during the year by an individual in the United States. The first award, for the year 1949, will be announced at the 17th annual convention of the Academy in New York, February 11, 1950. Those wishing to compete for this prize can secure further information from Dr. Walter Stuck, 1426 Nix Professional Bldg., San Antonio, Tex., Chairman of the Award Committee for 1949.

COATESVILLE, PENNSYLVANIA, VETERANS ADMINISTRATION HOSPITAL RECRUITING RESIDENTS IN NEUROLOGY

Several openings are available in the residency training program in neurology at the Veterans Administration Hospital, Coatesville, Pa. The program, organized by the Philadelphia Deans Committee, has been approved by the American Medical Association. This residency covers a period of three years or less, depending on the previous experience of an applicant, and is designed to prepare residents for certification in neurology by the American Board of Psychiatry and Neurology. The program includes rotation through the Veterans Administration Hospital, Coatesville, Pa., Veterans Administration Regional Office, Philadelphia, and the Philadelphia General Hospital. Applications should be sent to the Manager, Veterans Administration Hospital, Coatesville, Pa.

CANAL ZONE APPOINTMENTS OPEN

A limited number of Civil Service appointments are available in the Canal Zone for physicians interested in tropical medicine. The Panama Canal Health Department maintains a number of hospitals and dispensaries and supervises health conditions in the Zone as well as Colon and Panama City. There are excellent schools for the young. The beginning salary is $5,599.00 a year, plus free transportation to the Canal Zone, for physicians graduated from approved medical schools who have completed a year's internship in an approved hospital and been licensed in a State, and who are able to pass a standard physical examination. A beginning salary of $6,540.00 is offered to those who, in addition, have had a minimum of three years of medical practice.

A pamphlet, "The Panama Canal—Employment Information and Personnel Policies," may be had from the Chief of Office, The Panama Canal, Washington 25, D. C. Applications may be submitted to this officer or to the U. S. Civil Service Commission, Washington 25, D. C.

THE PHILADELPHIA COUNTY MEDICAL SOCIETY CELEBRATES ITS CENTENARY

On Wednesday, May 11, 1949, the Philadelphia County Medical Society of Pennsylvania celebrated its 100th year at a meeting and dinner at the Bellevue Stratford Hotel in Philadelphia. Dr. Richard A. Kern, F.A.C.P., President of the Society, presided, and greetings were received from Dr. F. F. Borzell, F.A.C.P., Speaker of the House of Delegates of the American Medical Association, from Dr. Gilson Colby Engel, President of the Medical Society of the State of Pennsylvania, and from Dr. T. Grier Miller, F.A.C.P., President of the College of Physicians of Philadelphia. The address of the evening was delivered by the Honorable Lister Hill, United States Senator from Alabama.

Dr. Spafford Ackerly, F.A.C.P., Professor of Psychiatry and head of the Department, University of Louisville Medical School, was one of the four taking part in the "Town Meeting of the Air" broadcast from Rochester, Minn., during Mental Health Week, in the latter part of April.

Willard Cole Rappleye, M.D., F.A.C.P., has been appointed Vice President in Charge of Medical Affairs of Columbia University. Dr. Rappleye has been Dean for many years of the College of Physicians and Surgeons of the University.

H. Corwin Hinshaw, Sr., M.D., F.A.C.P., formerly of the Mayo Clinic and Foundation, Rochester, Minn., has become Clinical Professor of Medicine in the Stanford University School of Medicine. Dr. Hinshaw's office will be located at 490 Post Street, San Francisco, Calif.

The Medical Society of the State of North Carolina celebrated its sesquicentennial at the annual session in Pinehurst early in May. Paul F. Whitaker, M.D., F.A.C.P., Kinston, A.C.P. Governor for North Carolina, served as moderator of a panel discussion and Joseph S. Hiatt, Jr. (Associate), McCain, N.C., was moderator of the symposium. The guest speaker was Hugh J. Morgan, M.D., F.A.C.P., Nashville, Tenn., 1947–48 President, whose subject was "Then and Now."

Aldrich C. Crowe, M.D., F.A.C.P., Ocean City, N. J., was made President-Elect of The Medical Society of New Jersey at the Society's recent meeting at Atlantic City. Sigurd W. Johnson, M.D., F.A.C.P., Passaic, and Harrold A. Murray, M.D., F.A.C.P., Newark, were elected First and Second Vice Presidents, respectively.

Brig. General James F. Simmons, (MC), U. S. A., Ret'd, F.A.C.P., Dean of the Harvard School of Public Health, and President of the Association of Schools of Public Health, has been elected Chairman of the Advisory Medical Board of the Leonard Wood Memorial of the American Leprosy Foundation. Dr. Simmons was recently awarded the Legion of Honor of the French Government recognizing his contributions during the war as Chief of the Preventive Medicine Service of the U. S. Army.

OBITUARIES

DR. W. HALSEY BARKER

On March 26, 1949, Dr. W. Halsey Barker, son of the late Dr. Lewellys F. Barker, died following a long illness at the Johns Hopkins Hospital.

Dr. Barker was born January 3, 1907, graduated from Princeton University with an A.B. degree in 1928, and entered that fall the Johns Hopkins University School of Medicine, from which he graduated in 1932. He served as House Officer at the Johns Hopkins Hospital from 1932 to 1935 and, after serving on the Staff of the Hospital of the Rockefeller Institute for Medical Research from 1935 to 1937, returned in 1937 as Resident in Medicine and later became Assistant Physician and Physician-in-Chief of the Clinic for Gastro-Intestinal and Nutritional Disorders.

Appointed Instructor in Medicine in the Johns Hopkins University School of Medicine in 1937, Dr. Barker became Assistant Dean in 1938 and Assistant Professor of Medicine in 1941.

Dr. Barker was elected to Associateship in the American College of Physicians in 1939, and to Fellowship in 1944. From 1942 to 1947 he served capably as Assistant Editor of the ANNALS OF INTERNAL MEDICINE. He was also a member of The Harvey Society, the American Clinical and Climatological Association and the American Medical Association.

Dr. Barker was an indefatigable worker, conscientious, and admired by all his friends. It is with a great sense of loss that we acknowledge his death; his place in our ranks will be difficult to fill.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. ALBERT RANKIN MARTIN

Dr. Albert Rankin Martin, of Chicago, Ill., died October 13, 1948.

Dr. Martin was born at Leer, Holland, in 1862. He graduated from Rush Medical College in 1892, and for many years served as Staff Physician at the St. Mary of Nazareth and Henrotin Hospitals in Chicago. He was a member of the Chicago Medical Society, the Illinois State Medical Society, the American Medical Association, and of the old American Congress on Internal Medicine, by virtue of which membership he became an Associate of the American College of Physicians in 1920.

DR. NATHANIEL EMMONS PAINE

Dr. Nathaniel Emmons Paine was born July 14, 1853, and died November 30, 1948, at the age of 95 years. He had been a Fellow of the American College of Physicians since 1920.

After graduating from Albany Medical College in 1875, Dr. Paine spent a year in postgraduate study in Vienna, and soon thereafter became interested in psychiatry. He was an assistant physician at the Middletown State Hospital for some years, and was Professor of Psychiatry of Boston University School of Medicine from 1887 to 1925, when he retired. Dr. Paine was a clear lecturer and a good teacher, and his students developed a real affection for him. His students knew that he always had a great and sincere interest in them.

Aside from his interest in medical teaching and the practice of psychiatry, he was the author of several books on genealogy, and received the Certificate of Merit in Genealogy of the Council of the Institute of American Genealogy in 1939.

Dr. Paine had a long and useful life, devoted to his specialty and to the training of young men who are following him in the important field of psychiatry.

DR. WILLIAM A. PLUMMER

Dr. William A. Plummer, of Rochester, Minn., died March 22, 1949.

Dr. Plummer was born June 30, 1883, at Racine, Minn. He received the degree of M.D. in 1910 from Northwestern University. He entered the Mayo Clinic as assistant in medicine in June, 1910, and became head of a section in medicine February 1, 1917. Later, he became associate professor of medicine in the University of Minnesota (Mayo Foundation), and senior consultant in a division of medicine of the Mayo Clinic. He was a fellow of the American College of Physicians (1928), and a member of the Minnesota Society of Internal Medicine, the Central Society for Clinical Research, the American Association for the Study of Goiter, the Association for the Study of Internal Secretions, the Southern Minnesota Medical Association, the American Medical Association and Sigma Xi.

Among William A. Plummer's outstanding characteristics were his kindliness and his friendliness to his patients and to his associates. He was an astute clinician and made many clinical observations of importance. Because of his retiring nature, he was more likely to impart these observations by word of mouth than through his writings. In this way he laid the foundation for many investigations, which he was glad to have carried out by others. His major interest, as was that of his brother, Henry S. Plummer, was in the field of thyroid disease, but his knowledge and ability in the clinical practice of medicine, generally, were very wide. He was unusually skilled in his observations on patients and carried their problems in his mind constantly until they were solved. His intense absorption in the problems of his patients was balanced by a fine sense of humor. He had keen insight into the psychological reactions of his patients and, also, those of his associates. This aided in giving him unusually good judgment in relation to the problems of the practice of medicine.

EDGAR V. ALLEN, M.D., F.A.C.P.,
Governor for Minnesota

DR. FREDERICK ERASTUS WARD

Dr. Frederick Erastus Ward, of Easton, Pa., died at his home on May 4, 1949.

Born in 1882, Dr. Ward attended Lafayette College and graduated from the Medico-Chirurgical College of Philadelphia in 1906.

Dr. Ward had civic as well as medical interest and was a former City Councilman of Easton. He had also served as Medical Inspector of the Public Schools of his home city, Chief of Staff of the Pennsylvania State Clinic for Tuberculosis, and the Baby Clinic of the Visiting Nurses' Association.

Dr. Ward was a member of his County and State Medical Societies and of the American Medical Association. In 1924 he was elected to membership in the American Congress on Internal Medicine and through this became an Associate of the American College of Physicians.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ROBERT OSGOOD BROWN

The untimely death of Robert Osgood Brown, M.D., F.A.C.P., on February 1, 1949, is a tragic loss to his professional colleagues and his many friends.

Dr. Brown was born February 13, 1890, in Chicago, Ill. He received his B.S. degree from the University of Chicago in 1912, and was graduated from Rush Medical College in June, 1914, interning at Cook County Hospital, Chicago, until June, 1916. He was an officer in the National Guard and served with the Pershing Expedition on the Mexican Border in 1916. He entered the practice of Medicine in Santa Fe, N. M., in 1916, specializing in internal medicine and diseases of the chest.

He became a Fellow of the American College of Physicians in 1932, and served as College Governor for New Mexico from 1942. He was also a Fellow of the American Medical Association and of the American College of Chest Physicians, and a member of the American Heart Association, American Trudeau Society and the New Mexico Clinical Society.

Dr. Brown was prominent in medical and civic affairs in New Mexico. He was formerly Associate Medical Director of Sunmount Sanatorium, staff member of St. Vincent Sanatorium and Hospital, founder and member of the Board of Directors of The Santa Fe Clinic and Foundation for Research and Treatment of Cancer, Santa Fe. He was actively interested in public health and welfare work in New Mexico, having served as Chairman of the New Mexico Public Welfare Board, Medical Consultant to the New Mexico Department of Public Welfare, and as Chairman of the Legislative Committee of the State Medical Society.

He was President of the Santa Fe County Tuberculosis Association at the time of his death; and had been President of the New Mexico Medical Society, and of the New Mexico Tuberculosis Association. The latter Association adopted the following Minute.

"Whereas Doctor Robert O. Brown's outstanding career in medicine and his untiring efforts to improve the health, social and economic welfare of his fellow citizens are matters of permanent record in the annals of New Mexico,

"Be it resolved that the New Mexico Tuberculosis Association and all its affiliated associations will ever remember and forever be indebted to Doctor Robert O. Brown for his untiring efforts in his official capacity as president from 1934 to 1937; his active participation as a member of its board of directors; his leadership and guidance in establishing the State Department of Public Health; his wise leadership as president of the Santa Fe County Tuberculosis Association and his capacity for friendship and personal interest in the problems, the welfare and the success of his fellow men."

Dr. Brown enjoyed an extensive and active practice. The community, his patients and his host of medical friends throughout the Southwest mourn his untimely death. We have lost a great and good friend and Doctor.

CARL H. GELLENTHIEN, M.D., F.A.C.P.

DR. ALPHONSE E. WALCH

Dr. Alphonse Edmund Walch of Minneapolis, Minn., a fellow of the American College of Physicians since 1942 and a diplomate of the American Board of Internal Medicine, died November 14, 1948, at the age of 42. Dr. Walch was a graduate of St. Mary's College, Winona, Minn., and of the St. Louis University School of Medicine. He was a member of the medical staffs of the Abbott, Minneapolis General and St. Mary's Hospitals.

DR. JAMES MURRAY WASHBURN

Dr. James Murray Washburn, Associate Professor of Medicine Emeritus of Northwestern University, died of carcinoma of the stomach on January 16, 1949, in his seventy-fifth year, at Lake Lure, N. C.

Dr. Washburn was born in Chicago on December 6, 1873. He received an A.B. degree from Harvard University in 1895, and an M.D. degree from Northwestern University Medical School in 1899. He was appointed a member of the Rush Medical College faculty in 1904, in which capacity he served until 1929, attaining the rank of Assistant Clinical Professor of Medicine. He served in the Army Medical Corps in World War I; when discharged, he held the rank of Lieutenant Colonel. From 1929 until 1934, he was an Associate Professor of Medicine at Northwestern University. From 1907 until 1929, he was a member of the Associate Staff of Presbyterian Hos-

pital. For many years, prior to the association of the Passavant Memorial Hospital with Northwestern University, he served on the staff of this institution and was a leader in the movement to reëstablish the Passavant Memorial Hospital in close affiliation with Northwestern University. In 1927, Dr. Washburn was elected Chief of Staff, a position to which he was reëlected annually until his retirement from practice in 1934.

Dr. Washburn was elected a Fellow of the American College of Physicians in 1934. He was also a Fellow of the American Medical Association, and a member of the Institute of Medicine, Chicago, the Chicago Society of Internal Medicine, and the Illinois State Medical Society. He was a past President of the Rutherford County, N. C., Medical Society.

Modest and unpretentious, James Murray Washburn was an able clinician and teacher, and a delightful companion with a droll sense of humor. Upon retirement from active practice in 1934, he moved to Lake Lure, situated in the Blue Ridge Mountains of North Carolina, where he had a summer home. He transformed this into the "Chalet Club" which became popular with people seeking beautiful scenery and rest.

His patients worshipped him and continue to complain that they cannot find anyone to take the place of this wise physician who believed that a specialist in Internal Medicine could render more satisfactory and effective service if he were also the "family doctor." His genial manner and kindly disposition will be missed by his colleagues and his many friends.

HOWARD B. CARROLL, M.D., F.A.C.P.

DR. OTTO ANDREW GEORGE REINHARD

Dr. Otto A. G. Reinhard, internist of Lincoln, Nebr., died on February 12, 1949. He was born in 1897 at Cullom, Ill., attended Wartburg Academy at Clinton, Iowa, and received from the University of Illinois the degrees of Bachelor of Science, 1920, and Doctor of Medicine, 1923. During World War I, he was a member of the Illinois Medical Units, S.A.T.C.

Following his interneship in the Cook County Hospital, Chicago, in 1923–1924, Dr. Reinhard served the Public Health Division of the Rockefeller Foundation for three years as Siamese Field Director. He then became a member of the Lincoln Clinic, Lincoln, Nebr., and served it until his death. He also held staff appointments to the Bryan Memorial and Lincoln General Hospitals. He was a diplomate of the American Board of Internal Medicine.

Dr. Reinhard was elected to Fellowship in the American College of Physicians in 1937. He was also a fellow of the American Medical Association, and a member of the American Heart Association, Association for the Study of Internal Secretions, Nebraska State Medical Association, and Lancaster County Medical Society.

J. D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. SAMUEL B. SCHOLZ

Samuel B. Scholz, M.D., F.A.C.P., was born in Dunn County, Wis., March 29, 1878, and died in Jenkintown, Pa., March 4, 1949.

Dr. Scholz attended Purdue University, the University of Michigan Medical School, for two years, and then the Denver and Gross College of Medicine, from which he received his M.D. degree in 1905. The field of Insurance Medicine can feel justly proud to have had Dr. Scholz enter it in 1907. He served in the Medical Department of the Equitable Life Insurance Society, 1907–17; as Medical Director of the Missouri State Life Insurance Company, from 1917 to 1919; as Associate Medical

Director of the Massachusetts Mutual Life Insurance Company, from 1919 to 1930; and as Medical Director of the Penn Mutual Life Insurance Company, Philadelphia, from 1930 until retirement in 1948.

Dr. Scholz was a Fellow of the American College of Physicians, since 1935, and of the American Medical Association. He was a former President of the Association of Life Insurance Medical Directors of America and Vice President of the International Life Insurance Medical Congress, 1938–1939. He also was a member of the Philadelphia and American Heart Associations.

Dr. Scholz was indeed a very fine and able physician and will be greatly missed by all who know him.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ADOLPH EMIL VOEGELIN

On February 22, 1949, Dr. Adolph E. Voegelin, of Detroit, Mich., died suddenly in his office. Dr. Voegelin was born in Philadelphia in 1894. He received his Bachelor's degree from Central High School, and his M.D. degree in 1916 from the Medico-Chirurgical College of Philadelphia. He became a Fellow of the American College of Physicians in 1924, and later a diplomate of the American Board of Internal Medicine. Dr. Voegelin's interest was chiefly in cardiology, and at the time of his death he was Chief of Staff of the Evangelical Deaconess Hospital, in Detroit, and Chief Cardiologist to the same institution.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

ANNALS OF INTERNAL MEDICINE

AUTHOR INDEX

Volume 30, January–June, 1949

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 30, January–June, 1949

ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS
Editor

PAUL W. CLOUGH
Assistant Editor

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CONTENTS

NUMBER 1, JANUARY, 1949

NUMBER 2, FEBRUARY, 1949

NUMBER 3, MARCH, 1949

NUMBER 4, APRIL, 1949

NUMBER 5, MAY, 1949

NUMBER 6, JUNE, 1949

Habitual Constipation of the Elderly

"Constipation in older individuals is so often accepted as a normal condition that much avoidable ill health and discomfort are permitted to afflict these patients."

—BERNSTEIN, W. C.: GERIATRICS 1:20 (MAY-JUNE) 1946

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ANNALS OF INTERNAL MEDICINE

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MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. DOE, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the ANNALS OF INTERNAL MEDICINE in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

EDITOR
MAURICE C. PINCOFFS, M.D.
University Hospital
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